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The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, and expression vectors for these DNAs as well as eukaryotic cells expressing these DNAs.

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DESCRIPTION

Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

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TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs encoding these proteins, and expression vectors for these DNAs as well as eukaryotic cells expressing these DNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against these proteins. The human cDNAs of the present invention can be utilized as probes for genetic diagnosis and gene sources for gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by these cDNAs. Cells into which these genes are introduced to express secretory proteins or membrane proteins in large quantity can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like.

BACKGROUND ART

Cells secrete many proteins extracellularly. These secretory proteins play important roles in the proliferation control, the differentiation induction, the material transport, the biophylaxis, and the like of the cells. Unlike intracellular proteins, the secretory proteins exert their actions outside the cells. Therefore, they can be administered in the intracorporeal manner such as the injection or the drip, so that they possess hidden

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potentialities as pharmaceuticals. In fact, a number of human secretory proteins such as interferons, interleukins, erythropoietin, thrombolytic agents and the like have been currently employed as pharmaceuticals. In addition, secretory proteins other than those described above are undergoing clinical trials for developing their use as pharmaceuticals. It is believed that the human cells produce many unknown secretory proteins. Availability of these secretory proteins as well as genes encoding them is expected to lead to development of novel pharmaceuticals utilizing these proteins.

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On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters and like in the material transport and transduction through the cell membrane. Examples thereof include receptors for various cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion and the like, transporters for saccharides and amino acids and the like. The genes for many of them have already been cloned. It has been clarified that abnormalities of these membrane proteins are involved in a number of previously cryptogenic diseases. Therefore, discovery of a new membrane protein is expected to lead to elucidation of the causes of many diseases, so that isolation of new genes encoding the membrane proteins has been desired.

Heretofore, due to difficulty in the purification from human cells, many of these secretory proteins and membrane proteins have been isolated by genetic approaches. A general method is the so-called expression cloning method, in which a cDNA library is introduced into eukaryotic cells to express cDNAs, and the cells secreting, or expressing on the surface of membrane, the protein having the activity of

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interest are then screened. However, only genes for proteins with known functions can be cloned by using this method.

In general, a secretory protein or a membrane protein possesses at least one hydrophobic domain within the protein. After synthesis in the ribosome, such domain works as a secretory signal or remains in the phospholipid membrane to be entrapped in the membrane. Accordingly, if the existence of a highly hydrophobic domain is observed in the amino acid sequence of a protein encoded by a cDNA when the whole base sequence of the full-length cDNA is determined, it is considered that the cDNA encodes a secretory protein or a membrane protein.

OBJECTS OF THE INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs encoding these proteins, and expression vectors for these DNAs as well as transformed eukaryotic cells that are capable of expressing these DNAs. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

25 BRIEF DESCRIPTION OF DRAWINGS

- Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02539.
- Fig. 2 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02770.
- Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02869.
 - Fig. 4 illustrates the hydrophobicity/hydrophilicity

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profile of the protein encoded by clone HP02956.

- Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02962.
- Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03014.
- Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10608.
- Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10609.
- 10 Fig. 9 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10611.
 - Fig. 10 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10617.
 - Fig. 11 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02837.
 - Fig. 12 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02991.
 - Fig. 13 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03063.
 - Fig. 14 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03091.
 - Fig. 15 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03092.
 - Fig. 16 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03116.
 - Fig. 17 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10618.
 - Fig. 18 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10619.
- Fig. 19 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10622.
 - Fig. 20 illustrates the hydrophobicity/hydrophilicity

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profile of the protein encoded by clone HP10625.

- Fig. 21 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02883.
- Fig. 22 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03140.
- Fig. 23 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10628.
- Fig. 24 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10629.
- 10 Fig. 25 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10635.
 - Fig. 26 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10636.
 - Fig. 27 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10640.
 - Fig. 28 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10644.
 - Fig. 29 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10656.
- 20 Fig. 30 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10672.
 - Fig. 31 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03194.
 - Fig. 32 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03219.
 - Fig. 33 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03236.
 - Fig. 34 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03237.
- Fig. 35 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03267.
 - Fig. 36 illustrates the hydrophobicity/hydrophilicity

profile of the protein encoded by clone HP03270.

Fig. 37 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03298.

Fig. 38 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10631.

Fig. 39 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10658.

Fig. 40 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10663.

Fig. 41 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03165.

Fig. 42 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03266.

Fig. 43 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP03287.

Fig. 44 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10665.

Fig. 45 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10669.

Fig. 46 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10670.

Fig. 47 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10671.

Fig. 48 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10673.

Fig. 49 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10675.

Fig. 50 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10683.

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SUMMARY OF THE INVENTION

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the result of intensive studies, the present inventors have successfully cloned cDNAs encoding proteins having hydrophobic domains from the human full-length cDNA bank, thereby completing the present invention. Thus, the present invention provides а human protein hydrophobic domain(s), namely a protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. Moreover, the present invention provides a DNA encoding the above-mentioned protein, exemplified by a cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120 and 131 to 150 as well as an expression vector that is capable of expressing such DNA by in vitro in eukaryotic cells and a transformed translation or eukaryotic cell that is capable of expressing such DNA and of producing the above-mentioned protein.

20 <u>DETAILED DESCRIPTION OF THE INVENTION</u>

The proteins of the present invention can be obtained, for example, by a method for isolating proteins from human organs, cell lines or the like, a method for preparing peptides by the chemical synthesis based on the amino acid sequence of the present invention, or a method for producing proteins by the recombinant DNA technology using the DNAs encoding the hydrophobic domains of the present invention. Among these, the method for producing proteins by the recombinant DNA technology is preferably employed. For example, the proteins can be expressed in vitro by preparing an RNA by in vitro transcription from a vector having the

cDNA of the present invention, and then carrying out in vitro translation using this RNA as a template. Alternatively, introduction of the translated region into a suitable expression vector by the method known in the art may lead to expression of a large amount of the encoded protein in prokaryotic cells such as Escherichia coli, Bacillus subtilis, etc., and eukaryotic cells such as yeasts, insect cells, mammalian cells, etc.

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In the case where the protein of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro by introducing the translated region of this cDNA into a vector having an RNA polymerase promoter, and then adding the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a wheat germ extract, which contains an RNA polymerase corresponding to the promoter. The RNA polymerase promoters are exemplified by T7, T3, SP6 and the like. The vectors containing these RNA polymerase promoters are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II and the like. Furthermore, the protein of the present invention can be expressed in the secreted form or the form incorporated in the microsome membrane when a canine pancreas microsome or the like is added to the reaction system.

In the case where the protein of the present invention is produced by expressing the DNA in a microorganism such as Escherichia coli etc., a recombinant expression vector in which the translated region of the cDNA of the present invention is introduced into an expression vector having an origin which is capable of replicating in the microorganism, a promoter, a ribosome-binding site, a cDNA-cloning site, a terminator and the like is constructed. After transformation

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of the host cells with this expression vector, the resulting transformant is grown, whereby the protein encoded by the cDNA can be produced in large quantity in the microorganism. In this case, a protein fragment containing any translated region can be obtained by adding an initiation codon and a termination codon in front of and behind the selected translated region to express the protein. Alternatively, the protein can be expressed as a fusion protein with another protein. Only the portion of the protein encoded by the cDNA can be obtained by cleaving this fusion protein with a suitable protease. The expression vectors for Escherichia coli are exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system and the like.

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In the case where the protein of the present invention is produced by expressing the DNA in eukaryotic cells, the protein of the present invention can be produced as a secretory protein, or as a membrane protein on the cellmembrane surface, by introducing the translated region of the cDNA into an expression vector for eukaryotic cells that has a promoter, a splicing region, a poly(A) addition site and the like, and then introducing the vector into the eukaryotic cells. The expression vectors are exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vectors, pRS, pYES2 and the like. Examples of eukaryotic cells to be used in general include mammalian cultured cells such as monkey kidney COS7 cells, Chinese hamster ovary CHO cells and the like, budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes and the like. Any eukaryotic cells may be used as long as they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eukaryotic cells by using a method

known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method and the like.

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After the protein of the present invention is expressed in prokaryotic cells or eukaryotic cells, the protein of interest can be isolated from the culture and purified by a combination of separation procedures known in the art. Examples of the separation procedures include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography and the like.

The proteins of the present invention also include peptide fragments (of 5 amino acid residues or more) containing any partial amino acid sequences in the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. These peptide fragments can be utilized as antigens for preparation of antibodies. Among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the protein of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal sequence [JP 8-187100 A]. Furthermore, some membrane proteins undergo the processing on the cell surface to be converted to the secreted forms. Such proteins or peptides in the secreted forms shall also come within the scope of the protein of the present invention. In the case where

sugar chain-binding sites are present in the amino acid sequences of the proteins, expression of the proteins in appropriate eukaryotic cells affords the proteins to which sugar chains are attached. Accordingly, such proteins or peptides to which sugar chains are attached shall also come within the scope of the protein of the present invention.

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The DNAs of the present invention include all the DNAs encoding the above-mentioned proteins. These DNAs can be obtained by using a method for chemical synthesis, a method for cDNA cloning and the like.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. The cDNAs are synthesized by using poly(A) RNAs extracted from human cells as templates. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method such as the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J., Gene 25: 263-269 (1983)] and the like. However, it is desirable to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available human cDNA libraries can be utilized. The cDNAs of the present invention can be cloned from the cDNA libraries by synthesizing an oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention and screening the cDNA libraries using this oligonucleotide as a probe for colony or plaque hybridization according to a method known in the art. In addition, the cDNA fragments of the present invention can be prepared from an mRNA isolated from human cells by the RT-

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PCR method in which oligonucleotides which hybridize with both termini of the cDNA fragment of interest are synthesized, which are then used as the primers.

The cDNAs of the present invention are characterized in that they comprise any one of the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or the base sequences represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Table 1 summarizes the clone number (HP number), the cells from which the cDNA clone was obtained, the total base number of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

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Table 1

		Table 1		
SEQ ID NO	HP	Cells	Base	Number of amino
	number		number	acid residues
1, 11, 21	HP02539	Saos-2	4485	647
2, 12, 22	HP02770	HT-1080	1509	350
3, 13, 23	HP02869	КВ	3059	206
4, 14, 24	HP02956	кв	2367	213
5, 15, 25	HP02962	КВ	2355	595
6, 16, 26	HP03014	Liver	1024	264
7, 17, 27	HP10608	Saos-2	1237	343
8, 18, 28	HP10609	кв	1332	244
9, 19, 29	HP10611	КВ	1932	303
10, 20, 30	HP10617	HT-1080	1124	160
31, 41, 51	HP02837	HT-1080	4473	1445
32, 42, 52	HP02991	кв	2630	582
33, 43, 53	нр03063	HT-1080	1472	410
34, 44, 54	HP03091	Liver	1652	483
35, 45, 55	HP03092	Liver	2112	607
36, 46, 56	HP03116	кв	1087	314
37, 47, 57	HP10618	HT-1080	1694	94
38, 48, 58	HP10619	HT-1080	1522	218
39, 49, 59	HP10622	Liver	1591	460
40, 50, 60	HP10625	Liver	1249	216
61, 71, 81	HP02883	КВ	4027	392
62, 72, 82	HP03140	HT-1080	2495	497
63, 73, 83	HP10628	HT-1080	1617	417
64, 74, 84	HP10629	WERI-RB	3269	649
65, 75, 85	HP10635	WERI-RB	458	93
66, 76, 86	HP10636	HT-1080	1712	425
67, 77, 87	HP10640	WERI-RB	1055	149
68, 78, 88	HP10644	WERI-RB	1616	396
69, 79, 89	HP10656	PMA-U937	1860	350
70, 80, 90	HP10672	Thymus	783	153
91, 101, 111	HP03194	КВ	3438	303

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92, 102, 112	HP03219	PMA-U937	1144	283
93, 103, 113	HP03236	HT-1080	2339	488
94, 104, 114	HP03237	HT-1080	1765	182
95, 105, 115	HP03267	Liver	1418	184
96, 106, 116	HP03270	PMA-U937	1211	140
97, 107, 117	HP03298	PMA-U937	1099	153
98, 108, 118	HP10631	WERI-RB	3489	173
99, 109, 119	HP10658	HT-1080	931	75
100, 110, 120	HP10663	PMA-U937	1123	159
121, 131, 141	HP03165	КВ	3234	636
122, 132, 142	HP03266	HT-1080	2490	318
123, 133, 143	HP03287	Thymus	1465	82
124, 134, 144	HP10665	HT-1080	917	247
125, 135, 145	HP10669	WERI-RB	1306	206
126, 136, 146	HP10670	WERI-RB	2022	432
127, 137, 147	HP10671	Thymus	1227	306
128, 138, 148	HP10673	Thymus	2210	555
129, 139, 149	HP10675	Thymus	1493	250
130, 140, 150	HP10683	PMA-U937	1264	174

The same clones as the cDNAs of the present invention can be easily obtained by screening the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention using an oligonucleotide probe synthesized on the basis of the base sequence of the cDNA provided in any one of SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120, and 131 to 150.

In general, the polymorphism due to the individual differences is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are added, deleted and/or substituted with other nucleotides in SEQ ID NOS: 11 to 30, 41 to 60, 71 to 90, 101 to 120, and 131 to 150 shall come within the scope of the present

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invention.

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Similarly, any protein in which one or plural amino acids are added, deleted and/or substituted with other amino acids resulting from the above-mentioned changes shall come within the scope of the present invention, as long as the protein possesses the activity of the protein having any one of the amino acid sequences represented by SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.

The cDNAs of the present invention also include cDNA fragments (of 10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or in the base sequences represented by SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use;

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as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source information to derive PCR primers for fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where polynucleotide encodes a protein which binds potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological

fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

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Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the

form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

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A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol.

149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

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proliferation Assays for and differentiation hematopoietic and lymphopoietic cells include, limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-Nordan, R. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 -Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors: Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

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Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including combined immunodeficiency (SCID)), regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may autoimmune disorders. More specifically, from infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania fungal infections such malaria spp. and various

candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

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Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic erythematosus, rheumatoid arthritis, autoimmune lupus pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia graft-versus-host gravis, disease and inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly or other respiratory problems. allergic asthma) Other which immune suppression is desired conditions, in (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited suppressing T cell responses or by inducing tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigenspecific and persists after exposure to the tolerizing agent

has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

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Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. achieve sufficient immunosuppression or tolerance in a

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subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

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The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. efficacy of blocking reagents in preventing or alleviating

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autoimmune disorders can be determined using a number of well-characterized animal models human of autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and (see murine experimental myasthenia gravis Paul Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

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Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the

transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

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In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor sarcoma, cells (e.g., melanoma, lymphoma, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For tumor cells obtained from a patient can example, transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the of the tumor cell provides the costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I lphachain protein and β , microglobulin protein or an MHC class

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II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

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The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte splenocyte or cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J.

Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

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Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Vitro Interscience (Chapter 3, In assays Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994;

Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell Zacharchuk, Immunology 66:233-243, 1991; Journal of 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

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A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells factor-dependent cell lines indicates or of involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to

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stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation mveloid cells such as granulocytes monocytes/macrophages (i.e., traditional CSF useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting proliferation of megakaryocytes growth and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such thrombocytopenia, and generally for use in place of or complementary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the abovementioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and

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Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bon is

not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

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A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and

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in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by а composition of the present invention contributes to repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendonligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

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The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, Alzheimer's, Parkinson's disease, Huntington's such as disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head

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trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. W095/16035 (bone, cartilage, tendon);

International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

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A protein of the present invention may also exhibit activinor inhibin-related activities. Inhibins characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among

other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

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A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial endothelial cells. and/or Chemotactic chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma tissues, as well as in treatment of localized infections. example, attraction of lymphocytes, monocytes For neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among

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other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke)).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include,

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without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

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A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/liqand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987;

Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

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Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cellcell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inhibiting promoting inflammatory process, orextravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, rejection, complement-mediated hyperacute nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly

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(such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

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A protein of the invention may also exhibit one or more following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body size or shape (such as, for example, augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or effecting the fertility of female subjects; male or effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors component(s); effecting orbehavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

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Examples

The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. procedures with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restriction enzymes and various modifying enzymes to be used were those available Takara Shuzo. The from compositions and the reaction conditions for each of the reactions were as described in the instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA library of fibrosarcoma cell line HT-1080 (WO 98/11217), the cDNA library of osteosarcoma cell line Saos-2 (WO 97/33993), the cDNA library of epidermoid carcinoma cell line KB (WO 98/11217) and the cDNA library of liver tissue delivered by the operation (WO 98/21328) were used as the

cDNA libraries. Additionally, the cDNA libraries constructed from phorbol ester-stimulated histiocytic lymphoma cell line U937 (ATCC CRL 1593) mRNA, human retinoblastoma cell line WERI-RB (ATCC HTB 169) mRNA and human thymus mRNA (Clontech) were also used. Full-length cDNA clones were selected from the respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA bank consisting of the full-length cDNA hydrophobicity/hydrophilicity profiles were determined for the proteins encoded by the full-length cDNA clones registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. A clone that has a hydrophobic region being assumed as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

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The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_NT rabbit reticulocyte lysate kit (Promega). In this case, [^{35}S]methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 μ l containing 12.5 μ l μ of T_NT rabbit reticulocyte lysate, 0.5 μ l of a buffer solution (attached to the kit), 2 μ l of an amino acid mixture (without methionine), 2 μ l of [^{35}S]methionine (Amersham) (0.37 MBq/ μ l), 0.5 μ l of T7 RNA polymerase, and 20 U of RNasin. The experiment in the presence of a membrane system was carried

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out by adding 2.5 μ l of a canine pancreas microsome fraction (Promega) to the reaction system. To 3 μ l of the reaction solution was added 2 μ l of the SDS sampling buffer (125 mM Tris-hydrochloride buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

10 (3) Expression in COS7

Escherichia coli cells harboring the expression vector for the protein of the present invention were cultured at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing $100~\mu\text{g/ml}$ of ampicillin, the helper phage M13K07 ($50~\mu$ l) was added, and the cells were then cultured at 37°C overnight. Single-stranded phage particles were obtained by polyethylene glycol precipitation from a supernatant separated by centrifugation. The particles were suspended in $100~\mu\text{l}$ of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from monkey kidney, COS7, were cultured at 37°C in the presence of 5% CO₂ in the Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum. 1 x 10 5 COS7 cells were inoculated into a 6-well plate (Nunc, well diameter: 3 cm) and cultured at 37°C for 22 hours in the presence of 5% CO₂. After the medium was removed, the cell surface was washed with a phosphate buffer solution followed by DMEM containing 50 mM Tris-hydrochloride (pH 7.5) (TDMEM). A suspension containing 1 μ l of the single-stranded phage suspension, 0.6 ml of the DMEM medium and 3 μ l of TRANSFECTAMTM (IBF) was added to the cells and the cells were cultured at 37°C for 3 hours in the presence of 5% CO₂. After the sample solution was removed,

the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the cells were cultured at 37°C for 2 days in the presence of 5% CO₂. After the medium was exchanged for a medium containing [³⁵S]cystine or [³⁵S]methionine, the cells were cultured for one hour. After the medium and the cells were separated each other by centrifugation, proteins in the medium fraction and the cell membrane fraction were subjected to SDS-PAGE.

(4) Clone Examples

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10 <HP02539> (SEQ ID NOS: 1, 11, and 21)

Determination of the whole base sequence of the cDNA insert of clone HP02539 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 188-bp 5'-untranslated region, a 1944-bp ORF, and a 2353-bp 3'-untranslated region. The ORF encodes a protein consisting of 647 amino acid residues and there existed a putative secretory signal at the N-terminus and six putative transmembrane domains at the C-terminus. Figure 1 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse frizzled-1 (GenBank Accession No. AF054623). Table 2 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse frizzled-1 (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the protein shared a homology of 90.4% in the entire

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region.

Table 2

	HP	MAEEEAPKKSRAAGGGASWELCAGALSARLTEEGSGDAGGRRPPVDPRRLARQLLLLLW
		****.**. * * * ****.* * * .******* *. *****
5	MM	MAEEAAPSESRAA-GRLSLELCAEALPGRREEVGHEDTASHRRPRADPRRWASGLLLLLW
	HP	LLEAPLILLGVRAQAAGQGPGQGPGPGQQPPPPPPQQQQSGQQYNGERGISVPDHGYCQPIS

	MM	LLEAPLLLGVRAQAAGQVSGPGQQAPPPPQPQQSGQQYNGERGISIPDHGYCQPIS
	HP	${\tt IPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCTVL}$
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	MM	IPLCTDMAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCTVL
	HP	${\tt EQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHGAGELCVGQNTSDKGTPTP}$

	MM	${\tt EQALPPCRSLCER} ARQGCE {\tt ALMNKFGFQWPDTLKCEKFPVHGAGELCVGQNTSDKGTPTP}$
15	HP	${\tt SLLPEFWTSNPQHGGGGHRGGFPGGAGASERGKFSCPRALKVPSYLNYHFLGEKDCGAPC}$
		********* *****.***. ******************
	MM	${\tt SLLPEFWISNGQHGGGGYRGGYPGGAGTVERGKFSCPRALRVPSYLNYHFLGEKDCGAPC}$
	HP	EPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSG

20	MM	EPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMPRFSYPERPIISLSG
	HP	CYTAVAVAYIAGFLLEDRVVCNDKFAEDGARTVAQGTKKEGCTILFMMLYFFSMASSIWW

	MM	CYTAVAVAYIAGFLLEDRVVCNDKFAEDGARTVAQGTNKEGCTILFMMLYFFSMASSIWW
	HP	VILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFVG
25		************
	MM	VILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFLG
	HP	LNNVDALRGFVLAPLFVYLFIGTSFILAGFVSLFRIRTIMKHDGTKTEKLEKLMVRIGVF

	MM	${\tt LNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKHDGTKTEKLEKLMVRIGVF}$
30	HP	${\tt SVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSYAIPCPHLQAGGGAPPHPPMSPDF}$

	MM	${\tt SVLYTVPATIVIACYFYEQAFRDQWERSWVAQSCKSYAIPCPHLQGGGGVPPHPPMSPDF}$
	HP	TVFMIKYLMTLIVGITSGFWIWSGKTLNSWRKFYTRLTNSKQGETTV

35	MM	TVFMIKYLMTLNSWRKFYTRLTNSKQGETTV

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA010020) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP02770> (SEQ ID NOS: 2, 12, and 22)

Determination of the whole base sequence of the cDNA insert of clone HP02770 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 252-bp 5'-untranslated region, a 1053-bp ORF, and a 204-bp 3'-untranslated region. The ORF encodes a protein consisting of 350 amino acid residues and there existed two putative transmembrane domains. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 42 kDa that was somewhat larger than the molecular weight of 38,274 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human RING zinc finger protein (GenBank Accession No. AF037204). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human RING zinc finger protein (ZN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue

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similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 56.0% in the entire region.

Table 3

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HP MHPAAFPLPVVVAAVLWGAAPTRGLIRATSDHNASMDFADLPALFGATLS .*** .*.*** ** *. ZN MILSIGMIMISATQVYTILTVQLFAFINLLPVEADILAYNFENASQTFDDLPARFGYRLP HP QEGLQGFLVEAHPDNACSPIAPPPPAPVNGSVFIALLRRFDCNFDLKVLNAQKAGYGAAV 10 .***.***....**.*.********* ZN AEGLKGFLINSKPENACEPIVPPPVKDNSSGTFIVLIRRLDCNFDIKVLNAQRAGYKAAI HP VHNVNSNELLNMVWNSEEIQQQIWIPSVFIGERSSEYLRALFVYEKGARVLLVPDNTFPL ****.*..* *. *. ..* *******.*.. *.. *.****.....*** 15 ZN VHNVDSDDLISMGSNDIEVLKKIDIPSVFIGESSANSLKDEFTYEKGGHLILVPEFSLPL HP GYYLIPFTGIVGLLVLAMGAVMIARCIOHRKRLORNRLTKEOLKQIPTHDYOKGDOYDVC ZN EYYLIPFLIIVGICLILIVIFMITKFVQDRHRARRNRLRKDQLKKLPVHKFKKGDEYDVC HP AICLDEYEDGDKLRVLPCAHAYHSRCVDPWLTQTRKTCPICKQPVHRGPGDED-QEEETQ 20 ****************************** ZN AICLDEYEDGDKLRILPCSHAYHCKCVDPWLTKTKKTCPVCKQKVVPSQGDSDSDTDSSQ HP GQEEGDEGEPRDHPASERTPLLGSSPTLPTSFGSLAPAPLVFPGPSTDPPLSPPSSPVIL ...* .* .* ZN EENEVTEHTPLLRPLASVSAQSFGALSESRSHQNMTESSDYEEDDNEDTDSSDAENEINE 25 HP V

ZN HDVVVQLQPNGERDYNIANTV

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA434312) among ESTs. However, since they are partial sequences, it can not be judged whether or

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not they encode the same protein as the protein of the present invention.

<HP02869> (SEQ ID NOS: 3, 13, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP02869 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 229-bp 5'-untranslated region, a 621-bp ORF, and a 2209-bp 3'-untranslated region. The ORF encodes a protein consisting of 206 amino acid residues and there existed two putative transmembrane domains. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost identical with the molecular weight of 22,367 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA278247) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

25 <HP02956> (SEQ ID NOS: 4, 14, and 24)

Determination of the whole base sequence of the cDNA insert of clone HP02956 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 68-bp 5'-untranslated region, a 642-bp ORF, and a 1657-bp 3'-untranslated region. The ORF encodes a protein consisting of 213 amino acid residues and there existed three putative transmembrane domains. Figure 4

depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was almost identical with the molecular weight of 23,902 predicted from the ORF. When expressed in COS7 cells, an expression product of about 20 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human tetraspan NET-4 (GenBank Accession No. AF065389). Table 4 shows the comparison. between amino acid sequences of the human protein of the present invention (HP) and the human tetraspan NET-4 (TS). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 58.8% in the C-terminal region of 119 amino acid residues.

Table 4

HP MHY TS MSGKHYKGPEVSCCIKYFIFGFNVIFWFLGITFLGIGLWAWNEKGVLSNISSITDLGGFD 5 HP YRYSNAKVSCWYKYLLFSYNIIFWLAGVVFLGVGLWAWSEKGVLSDLTKVTRMHGIDPVV TS PVWLFLVVGGVMFILGFAGCIGALRENTFLLKFFSVFLGIIFFLELTAGVLAFVFKDWIK HP LVLMVGVVMFTLGFAGCVGALRENICLLNFNQCCGAYGPEDWDLNVYFNCSGASYSREKC .. ****.*.**.***** 10 TS DQLYFFINNNIRAYRDDIDLQNLIDFTQEYWQCCGAFGADDWNLNIYFNCTDSNASRERC HP GVPFSCCVPDPAQKVVNTQCGYDVRIQLKSKWDESIFTKGCIQALESWLPRNIYIVAGVF TS GVPFSCCTKDPAEDVINTOCGYDAROKPEVDQQIVIYTKGCVPQFEKWLQDNLTIVAGIF 15 HP IAISLLOIFGIFLARTLISDIEAVKAGHHF *.*.****** **..*.**** TS IGIALLQIFGICLAQNLVSDIEAVRASW

20 Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T05279) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP02962> (SEQ ID NOS: 5, 15, and 25)

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Determination of the whole base sequence of the cDNA insert of clone HP02962 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 19-bp 5'-untranslated region, a 1788-bp ORF, and a 548-bp 3'-untranslated region. The ORF encodes a

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protein consisting of 595 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 70 kDa that was somewhat larger than the molecular weight of 67,549 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 85 kDa to which sugar chains are presumably attached. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from alanine at position 23. In addition, there exist in the amino acid sequence of this protein four sites at which Nglycosylation may occur (Asn-Thr-Thr at position 75, Asn-Gln-Thr at position 153, Asn-Tyr-Thr at position 237 and Asn-Ser-Ser at position 360).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human hypothetical protein KIAA0584 (GenBank Accession No. AB011156). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human hypothetical protein KIAA0584 (KI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 52.9% in the entire region.

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Table 5

	HP	MRAARAAPLLQLLLLLGPWLEAAGVAESPLPAVVLAILARNAEHSL
		**** *.*.*.*.*.*.
5	KI	${\tt LAWSLLLLSSALLREGCRARFVAERDSEDDGEEPVVFPESPLQSPTVLVAVLARNAAHTL}$
	HP	PHYLGALERLDYPRARMALWCATDHNVDNTTEMLQEWLAAVGDDYAAVVWRPEGEPRFYP
		. *** * * * ****** * * * * * *
	KI	PHFLGCLERLDYPKSRMAIWAATDHNVDNTTEIFREWLKNVQRLYHYVEWRPMDEPESYP
	HP	${\tt DEEGPKHWTKERHQFLMELKQEALTFAR-NWGADYILFADTDNILTNNQTLRLLMGQGLP}$
10		** ***** * . * . * . * . * . *
	KI	${\tt DEIGPKHWPTSRFAHVMKLRQAALRTAREKW-SDYILFIDVDNFLTNPQTLNLLIAENKT}$
	HP	${\tt VVAPMLDSQTYYSNFWCGITPQGYYRTAEYFPTKNRQRRGCFRVPMVHSTFLASLRAEG}$
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	KI	IVAPMLESRGLYSNFWCGITPKGFYKRTPDYVQIREWKRTGCFPVPMVHSTFLIDLRKEA
15	HP	${\tt ADQLAFYPPHPNYTWPFDDIIVFAYACQAAGVSVHVCNEHRYGYMNVPVKSHQGLEDERV}$
		.*.*.******.***
	KI	${\tt SDKLTFYPPHQDYTWTFDDIIVFAFSSRQAGIQMYLCNREHYGYLPIPLKPHQTLQEDIE}$
	HP	$\tt NFIHLILEALVDGPRMQASAHVTRPSKRPSKIGFDEVFVISLARRPDRRERMLASLWEME$
		*.****. * .*** *.*.*.*.* ** ** *
20	KI	NLIHVQIEAMIDRPPMEPSQYVSVVPKYPDKMGFDEIFMINLKRRKDRRDRMLRTLYEQE
	HP	ISGRVVDAVDGWMLNSSAIRNLGVDLLPGYQDPYSGRTLTKGEVGCFLSHYSIWEEVVAR
		.* **.*****.***.**.*******
	KI	IEVKIVEAVDGKALNTSQLKALNIEMLPGYRDPYSSRPLTRGEIGCFLSHYSVWKEVIDR
	HP	GLARVLVFEDDVRFESNFRGRLERLMEDVEAEKLSWDLIYLGRKQVN-PEKETAVEGLPG
25		****.****** .** .***.*.*.**.**
	KI	ELEKTLVIEDDVRFEHQFKKKLMKLMDNIDQAQLDWELIYIGRKRMQVKEPEKAVPNVAN
	HP	LVVAGYSYWTLAYALRLAGARKLLASQPLRRMLPVDEFLPIMFDQHPNEQYKAHFWPRDL
		** *.*****.**********.**
	KI	LVEADYSYWTLGYVISLEGAQKLVGANPFGKMLPVDEFLPVMYNKHPVAEYKEYYESRDL
30	HP	VAFSAQPLLAAPTHYAGDAEWLSDTETSSPWDDDSGRLISWSGSQKTLRSPRLDLTGS
		****.*** ****.*******. ****
	KI	KAFSAEPLLIYPTHYTGQPGYLSDTETSTIWDNETV-ATDWDRTHAWKSRKQSRIYSNAK
	HP	SGHSLQPQPRDEL
		.
35	KI	NTEALPPPTSLDTVPSRDEL

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA358896) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP03014> (SEQ ID NOS: 6, 16, and 26)

Determination of the whole base sequence of the cDNA insert of clone HP03014 obtained from cDNA library of human liver revealed the structure consisting of a 26-bp 5'untranslated region, a 795-bp ORF, and a 203-bp 3'untranslated region. The ORF encodes a protein consisting of 264 amino acid residues and there existed one putative 6 depicts transmembrane domain. Figure hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, the present protein. of translation resulted in formation of a translation product of 31 kDa that was somewhat larger than the molecular weight of 28,471 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse WW domain-binding protein 1 (GenBank Accession No. U40825). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse WW domain-binding protein 1 (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue

similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 85.1% in the entire region.

Table 6

HP MVASAKMGRAGTMAVAAELR ${\tt MM} \ \ {\tt MARASSRNSSEE} {\tt AWGSLQAPQQQQSPAASSLEGAIWRRAGTQTRALDTILYHPQQSHLLR}$ HP ELCPGVNNQPYLCESGHCCGETGCCTYYYELWWFWILWTVLILFSCCCAFRHRRAKLRLQ 10 *********** MM ELCPGVNTOPYLCETGHCCGETGCCTYYYELWWFWLLWTVLILFSCCCAFRHRRAKLRLQ HP QQQRQREINLLAYHGACHGAGPFPTGSLLDLRFLSTFKPPAYEDVVHRPGTPPPPYTVAP ********* MM QOOROREINLLAYHGACHGAGPVPTGSLLDLRLLSAFKPPAYEDVVHHPGTPPPPYTVGP 15 HP GRPLTASSEQTCCSSSSSCPAHFEGTNVEGVSSHQSAPPHQEGEPGAGVTPASTPPSCRY MM GYPWTTSSECTRCSSESSCSAHLEGTNVEGVSSQQSALPHQEGEPRAGLSPVHIPPSCRY HP RRLTGDSGIELCPCPASGEGEPVKEVRVSATLPDLEDYSPCALPPESVPQIFPMGLSSSE 20 ***********

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HP GDIP

MM GTSHK

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W24575) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

MM RRLTGDSGIELCPCPDSSEGEPLKEARASASQPDLEDHSPCALPPDSVSQVPPMGLASSC

<HP10608> (SEQ ID NOS: 7, 17, and 27)

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Determination of the whole base sequence of the cDNA insert of clone HP10608 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 23-bp 5'-untranslated region, a 1032-bp ORF, and a 182-bp 3'-untranslated region. The ORF encodes a protein consisting of 343 amino acid residues and there existed five putative transmembrane domains. Figure 7 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 37 kDa that was somewhat smaller than the molecular weight of 40,584 predicted from the ORF. When expressed in COS7 cells, an expression product of about 36 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T35406) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10609> (SEQ ID NOS: 8, 18, and 28)

Determination of the whole base sequence of the cDNA insert of clone HP10609 obtained from cDNA library of the human epidermoid carcinoma cell line KB revealed the structure consisting of a 38-bp 5'-untranslated region, a 735-bp ORF, and a 559-bp 3'-untranslated region. The ORF encodes a protein consisting of 244 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 8 depicts the hydrophobicity/hydrophilicity

profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 27,756 predicted from the ORF. When expressed in COS7 cells, an expression product of about 26 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Mycobacterium tuberculosis hypothetical protein Rv1147 (GenBank Accession No. Z95584). Table 7 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Mycobacterium tuberculosis hypothetical protein Rv1147 (MT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 31.7% in the entire region.

Table 7

HP MDILVPILOLLVLLLTLPLHLMALLGCWOPLCKSYFPYLMAVLTPKSNRKMESKKRELFS 5 MT MTSGAAASASRVDHPLFARIWPVVAAHEAEAIRAL HP QIKGLTGASGKVALLELGCGTGANFQFYPPGC-RVTCLDPNPHFEKFLTKSMAENRHLQY *.* **.* **.* *.*.** . .*. ..*.*... MT RRENLAGLSGRV--LEVGAGVGTNFAYYPVAVEQVIAMEPEPRLAA-KARIAAADAPVPI HP ERFVVAPGEDMRQLADGSMDVVVCTLVLCSVQSPRKVLQEVRRVLRPGGVLFFWEHVAEP 10 MT -VVTDKTVEEFRD--TETFDAVVCSLVLCSVSDPGAVLAHLRSLLRRGGELRYLEHVASA HP YGSWAFMWQQVFEPTWKHIGDGCCLTRETWKDLENAQFSEIQMERQPPPLKW--LPVGPH *... . . * .. ** *.** * MT -GARGRVORFVDATFWPRLAGNCHTHRHTERAILDAGFVVDSSRREWAFPAWVPLPVSEL HP IMGKAVK 15 .*.* . MT ALGRAHRT

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T60981) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10611> (SEQ ID NOS: 9, 19, and 29)

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Determination of the whole base sequence of the cDNA insert of clone HP10611 obtained from cDNA library of the human epidermoid carcinoma cell line KB revealed the structure consisting of a 37-bp 5'-untranslated region, a 912-bp ORF, and a 983-bp 3'-untranslated region. The ORF

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encodes a protein consisting of 303 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 31 kDa that was somewhat smaller than the molecular weight of 33,856 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 36 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 34. When expressed in COS7 cells, an expression product of about 35 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the 218 amino acid residues at the C-terminus of the protein matched with the amino acid sequence of human glucosidase II (SWISS-PROT Accession No. Q06003). However, no similarity was observed at the N-terminal portion.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H14054) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10617> (SEQ ID NOS: 10, 20, and 30)

Determination of the whole base sequence of the cDNA insert of clone HP10617 obtained from cDNA library of the human fibrosarcoma cell line HT-1080 revealed the structure

consisting of a 72-bp 5'-untranslated region, a 483-bp ORF, and a 569-bp 3'-untranslated region. The ORF encodes a protein consisting of 160 amino acid residues and there existed four putative transmembrane domains. Figure 10 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight. When expressed in COS7 cells, an expression product of about 17 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H67672) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP02837> (SEQ ID NOS: 31, 41, and 51)

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Determination of the whole base sequence of the cDNA insert of clone HP02837 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 44-bp 5'-untranslated region, a 4338-bp ORF, and a 91-bp 3'-untranslated region. The ORF encodes a protein consisting of 1445 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 11 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 150 kDa that was almost identical with the molecular weight of 161,657 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the

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cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from valine at position 22. In addition, there exist in the amino acid sequence of this protein 18 sites at which N-glycosylation may occur.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human α -2 macroglobulin (SWISS-PROT Accession No. P01023). Table 8 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human α -2 macroglobulin (MG). Therein, the marks of - and * represent a gap and an amino acid residue identical with that of the protein of the present invention, respectively. The both proteins shared a homology of 29.5% in the entire region.

Table 8

	HP	MQGPPLLTAAHLLCVCTAALA-VAPGPRFLVTAPGIIRPGGNVTIGVELLEHCPSQVT
		* ** ** * * * * * * * *
5	MG	${\tt MGKNKLLHPSLVLLLLVLLPTDASVSGKPQYMVLVP-SLLHTETTEKGCVLLSYLNETVT}$
	HP	VKAELLKTASN-LTVSVLEAE-GVFEKGSFKTLTLPSLPLNSADEIYELRVTGRTQDEIL
		* * * * * * * * * * * * * * * * * * * *
	MG	VSASLESVRGNRSLFTDLEAENDVLHCVAFAVPKSSSNEEVMFLTVQVKGPTQE
	HP	FSNSTRLSFETKRISVFIQTDKALYKPKQEVKFRIVTLFSDFKPYKTSLNILIKDPKS
10		* * * **** *** * * * * * * * * * *
	MG	FKKRTTVMVKNEDSLVFVQTDKSIYKPGQTVKFRVVSMDENFHP-LNELIPLVYIQDPKG
	HP	NLIQQWLSQQSDLGVISKTFQLSSHPILGDWSIQVQ-VNDQTYYQSFQVSEYVLPKFEVT
		* * * * * * * * * * * * * * * * * * * *
	MG	${\tt NRIAQWQSFQLEGGLKQFSFPLSSEPFQGSYKVVVQKKSGGRTEHPFTVEEFVLPKFEVQ}$
15	HP	$\verb LQTPLYCSMNSKHLNGTITAKYTYGKPVKGDVTLTFLPLSFWGKKKNITKTFKING $
		* * * ****** * * * * *
	MG	${\tt VTVPKIITILEEEMNVSVCGLYTYGKPVPGHVTVSICRKYSDASDCHGEDSQAFCEKFSG}$
	HP	SANFSFNDEEMKNVMDSSNGLSEY-LDLSFPGPVEILTTVTESVTGISRNVSTNVF
		* ** * ** *
20	MG	QLNSHGCFYQQVKTKVFQLKRKEYEMKLHTEAQIQEEGTVVELTGRQSSEITRTITKLSF
	HP	FKQHDYIIEFFDYTTVLKPSLNFTATVKVTRADGNQLTLEERRNNVVITVTQRNYTEY
		* * * * * * * *
	MG	VKVDSHFRQGIPFFGQVRLVDGKGVPIPNKVIFIRGNEANYYSNATTDEHGLV
	HP	WSGSNSGNQKMEAVQKINYTVPQSGTFKIEFPILEDSSELQLKAYFLGSKSSMAVHSLFK
25		* * * * * * * * * * * * * * * * * * * *
	MG	QFSINTTN-VMGTSLTVRVNYKDRSPCYGYQWVSEEHEEAHHTAYLVFSPSKSFVHLEPM
	HP	SPSKTYIQLKTRDENIKVGSPFELVVSGNKRLKELSYMVVSRGQLVAVGKQNSTMF
		* * * * * * * * *
	MG	SHELPCGHTQTVQAHYILNGGTLLGLKKLSFYYLIMAKGGIVRTGTHGLLVKQEDMKGHF
30	HP	S-LTPENS-WTPKACVIVYYIEDDGEIISDVLKIPVQLVFKNKIKLYWSKVKAEPSEKVS
		* * * * * * * * * * * * * *
	MG	SISIPVKSDIAPVARLLIYAVLPTGDVIGDSAKYDVENCLANKVDLSFSPSQSLPASHAH
	HP	LRISVT-QPDSIVGIVAVDKSVNLMNASNDITMENVVHEL-ELYNTG
		** ** * * *** ** * * * * *
25	MG	LRVTAAPOSVCALRAVDOSVLLMKPDAELSASSVYNLLPEKDLTGFPGPLNDODDEDC

	HP	PYYLGMFMNSFAVFQE-CGLWVLTDANLTKDYIDGVYDNAEYAERF1	MEENE
		** * ** * * *	* **
	MG	G INRHNVYINGITYTPVSSTNEKDMYSFLEDMGLKAFTNSKIRKPKMCPQLQQYEN	MHGPE
	HP	P HIVDIHDFSLGSSPHVRKHFPETWIWLDTNMGSRIYQEFEV	EVPDS1
5		* ** *** ***** * * * *	***
	MG	G LRVGFYESDVMGRGHARLVHVEEPHTETVRKYFPETWIWDLVVVNSAGVAEVGV	ITCGVI
	HP	P TSWVATGFVISEDLGLGLTTTPVELQAFQPFFIFLNLPYSVIRGEEFALEITIFN	VYLKDA
		* * * * *** *** * * ****** * ******* * *	***
	MG	G TEWKAGAFCLSEDAGLGISST-ASLRAFQPFFVELTMPYSVIRGEAFTLKATVLN	VYLPKC
10	HP	P TEVKVIIEKSDKFDILMTSSEINATGHQ-QTLLVPSEDGATVLFPIRPTH	ILGE
		** * * * * * * * * * * * * * * * * * * *	* *
	MG	G IRVSVQLEASPAFLAVPVEKEQAPHCICANGRQTVSWAVTPKSLGNVNFTVSAE	LESQE
	HP	P IPITVTALSPTASDAITQMILVKAEGIEKSYSQSILLDLTDNRLQSTLKTLSF	SFPPN
		* * * * ** ** **	***
15	MG	LCGTEVPSVPEHGRKDTVIKPLLVEPEGLEKETTFNSLLCPSGGEVSEELSI	KLPPN
	HP	P TVTGSERVQITAIGDVLGPSINGLASLIRMPYGCGEQNMINFAPNIYILDYLTKK	KQLTD
		* * * * * * * * * * * * * * * * * * * *	***
	MG	VVEESARASVSVLGDILGSAMQNTQNLLQMPYGCGEQNMVLFAPNIYVLDYLNET	QQLTP
	HP	P NLKEKALSFMRQGYQRELLYQREDGSFSAFG—NYDPSGSTWLSAFVLRCFLEAD	PYIDI
20		* **	** *
	MG	S EVKSKAIGYLNTGYQRQLNYKHYDGSYSTFGERYGRNQGNTWLTAFVLKTFAQAR	AYIFI
	HP	P DQNVLHRTYTWLKGHQKSNGEFWDPGRVIHSELQGGNKSPVTLTAYIVTSLLGYR	KYQPN
		* ** ** ** * ** *** **	
	MG	DEAHITQALIWLSQRQKDNGCFRSSGSLLNNAIKGGVEDEVTLSAYITIALLEIP	LTVTH
25	HP	P IDVQESIHFLESEFSRGISDNYTLALITYALSSVG-SPKAKEALNMLTW	RAEQE
	•	* *** * * * * * * * * * * * *	*
	MG	PVVRNALFCLESAWKTAQEGDHG-SHVYTKALLAYAFALAGNQDKRKEVLKSLNE	EAVKK
	HP	GGMQFWVSSESKLSDSWQPRSLDIEVAAYALLSHFLQFQTSEGI	PIMRW
		* * * * * **	* *
30	MG	DNSVHWERPQKPKAPVGHFYEPQAPSAEVEMTSYVLLAYLTAQPAPTSEDLTSAT	NIVKW
	HP	LSRQRNSLGGFASTQDTTVALKALSEFAALMNTERTNIQVTVTGPSS-PSPVKFL	IDTHN
		* * *** **** *** * * * * * * * *	* *
	MG	ITKQQNAQGGFSSTQDTVVALHALSKYGAATFT-RTGKAAQVTIQSSGTFSSKFQ	VDNNN
	HP	RILLLQTAELAVVQPTAVNISANGFGFAICQLNVVYNVKASGSSRRRRSIQNQEAF	DLDVA
35		**** * * * * *	*

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MG RLLLQQVSL-PELPGEYSMKVTGEGCVYLQTSLKYN----ILPEKEEFPFALGVQTLPQT HP VKENK-DDLNHVDLNVCTSFSGPGRSGMALMEVNLLSGFMVPSEAISLSETVKKVEYDHG * ** MG CDEPKAHTSFQISLSVSYTGS-RSASNMAIVDVKMVSGF-----IPLKPTVKMLE----HP KLNLYLDSVNETQFCVNIPAVRNFKVSNTQDASVSIVDYYEPRRQAVRSYNSEVKLSSCD 5 MG ----RSNHVSRTEVSSNHVLIYLDKVSNOTLSLFFTVLODVP----VR-----D HP LCSDVQGCRPCEDGASGSHHHSSVIFIFCFKLLYFMELWL 10 MG L---KPAIVKVYDYYETDEFAIAEYNAPCSKDL----GNA

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W33075) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP02991> (SEQ ID NOS: 32, 42, and 52)

Determination of the whole base sequence of the cDNA insert of clone HP02991 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 81-bp 5'-untranslated region, a 1749-bp ORF, and a 800-bp 3'-untranslated region. The ORF encodes a protein consisting of 582 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 12 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 66 kDa that was somewhat larger than the molecular weight of 64,244 predicted from the ORF. In

this case, the addition of a microsome led to the formation of a product of 78 kDa to which sugar chains are presumably attached. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from valine at position 27. In addition, there exist in the amino acid sequence of this protein seven sites at which N-glycosylation may occur (Asn-Gly-Thr at position 70, Asn-Gly-Thr at position 182, Asn-Gly-Ser at position 294, Asn-His-Thr at position 310, Asn-Gly-Thr at position 352, Asn-Glu-Thr at position 393 and Asn-Cys-Ser at position 407).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse FKBP65-binding protein (GenBank Accession No. L07063). Table 9 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse FKBP65-binding protein (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 88.8% in the entire region.

Table 9

	HP	${\tt MFPAGPPSHSLLRLPLLQLLLLVVQAVGRGLGRASPAGGPLEDVVIERYHIPRACPREVQ}$
		** .**. * * * **************
5	MM	${\tt MFLVGSSSHTLHRVRILPLLLL-LQTLERGLGRASPAGAPLEDVVIERYHIPRACPREVQ}$
	HP	${\tt MGDFVRYHYNGTFEDGKKFDSSYDRNTLVAIVVGVGRLITGMDRGLMGMCVNERRRLIVP}$

	MM	${\tt MGDFVRYHYNGTFEDGKKFDSSYDRSTLVAIVVGVGRLITGMDRGLMGMCVNERRRLIVP}$
	HP	${\tt PHLGYGSIGLAGLIPPDATLYFDVVLLDVWNKEDTVQVSTLLRPPHCPRMVQDGDFVRYH}$
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	MM	${\tt PHLGYGSIGVAGLIPPDATLYFDVVLLDVWNKADTVQSTILLRPPYCPRMVQNSDFVRYH}$
	HP	${\tt YNGTLLDGTSFDTSYSKGGTYDTYVGSGWLIKGMDQGLLGMCPGERRKIIIPPFLAYGEK}$
		********.**.**.***.*****************
	MM	${\tt YNGTLLDGTGFDNSYSRGGTYDTYIGSGWLIKGMDQGLLGMCPGEKRKIIIPPFLAYGEK}$
15	HP	${\tt GYGTVIPPQASLVFHVLLIDVHNPKDAVQLETLELPPGCVRRAGAGDFMRYHYNGSLMDG}$

	MM	${\tt GYGTVIPPQASLVFYVLLLDVHNPKDTVQLETLELPQGCVRRAVAGDFMRYHYNGSLMDG}$
	HP	${\tt TLFDSSYSRNHTYNTYIGQGYIIPGMDQGLQGACMGERRRITIPPHLAYGENGTGDKIPG}$

20	MM	${\tt TLFDSSYSRNHTYNTYVGQGYIIPGMDQGLQGACIGERRRITVPPHLAYGENGTGDKIPG}$
	HP	${\tt SAVLIFNVHVIDFHNPADVVEIRTLSRPSETCNETTKLGDFVRYHYNCSLLDGTQLFTSH}$
		*****.********.* ***.****.*.*.**.**.**.*
	MM	SAVLIFDVHVIDFHNPSDPVEIKTLSRPPENCNETSKIGDFIRYHYNCSLLDGTRLFSSH
	HP	DYGAPQEATLGANKVIEGLDTGLQGMCVGERRQLIVPPHLAHGESGARGVPGSAVLLFEV
25		**.*** ******** *******************
	MM	DYEAPQEITLGANKVIEGLDRGLQGMCVGERRQLIVPPHLAHGENGARGVPGSAVLLFEV
	HP	${\tt ELVSREDGLPTGYLFVWHKDPPANLFEDMDLNKDGEVPPEEFSTFIKAQVSEGKGRLMPG}$

	MM	ELVSREDGLPTGYLFVWYQDPSTSLFEDMDLNKDGEVPPEEFSSFIKAQVNEGKGRLMPG
30	HP	QDPEKTIGDMFQNQDRNQDGKITVDELKLKSDEDEERVHEEL
		.********
	MM	QDPDKTISDMFQNQDRNQDGKITAEELKLKSDEDQERVHEEL

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sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA308536) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03063> (SEQ ID NOS: 33, 43, and 53)

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Determination of the whole base sequence of the cDNA insert of clone HP03063 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 88-bp 5'-untranslated region, a 1233-bp ORF, and a 151-bp 3'-untranslated region. The ORF encodes a protein consisting of 410 amino acid residues and there existed a putative transmembrane domain at the N-terminus. Figure 13 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 46 kDa that was almost identical with the molecular weight of 45,786 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse AUP1 (GenBank Accession No. U41736). Table 10 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse AUP1 (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 90.2% in the entire region.

Table 10

HP MELPSGPGPERLFDSHRLPGDCFLLLVLLLYAPVGFCLLVLRLFLGIHVFLVSCALPDSV MM MEPPPAPGPERLFDSHRLPSDGFLLLALLLYAPVGLCLLVLRLFLGLHVFLVSCALPDSV 5 HP LRRFVVRTMCAVLGLVARQEDSGLRDHSVRVLISNHVTPFDHNIVNLLTTCSTPLLNSPP ************ MM LRRFVVRTMCAVLGLVARQEDSGLRDHRVRVLISNHVTPFDHNIVNLLTTCSTPLLNSPP HP SFVCWSRGFMEMNGRGELVESLKRFCASTRLPPTPLLLFPEEEATNGREGLLRFSSWPFS ********** 10 MM SFVCWSRGFMEMDRRVELVESLKKFCASTRLPPTPLLLFPEEEATNGREGLLRFSSWPFS HP IODVVOPLTLOVORPLVSVTVSDASWVSELLWSLFVPFTVYQVRWLRPVHROLGEANEEF ************************* MM IODVVOPLTLOVORPLVSVTVSDASWVSELLWSLFVPFTVYOVRWLHPIRROLGEESEEF 15 HP ALRVOOLVAKELGOTGTRLTPADKAEHMKRORHPRLRPQSAQSSFPPSPGPSPDVQLATL ****************************** MM ALRVQQLVAKELGQIGTRLTPADKAEHMKRQRHPRLRPQSVQSSFPSPPSPSSDVQLTTL HP AORVKEVLPHVPLGVIORDLAKTGCVDLTITNLLEGAVAFMPEDITKGTQSLPTASASKF 20 MM AHRVKEVLPHVPLNVIORDLARTGCVDLTITNLLEGAVAFMPEDVTEGSQSPPAPSAPKF HP PSSGPVTPOPTALTFAKSSWAROESLOERKOALYEYARRRFTERRAQEAD **** *********************** MM PSSGLATPQPTALTFAKSSWARQESLQERKQALYEYARRRFRERQAQEAE

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA131932) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

Determination of the whole base sequence of the cDNA insert of clone HP03091 obtained from cDNA library of human liver revealed the structure consisting of a 16-bp 5'-untranslated region, a 1452-bp ORF, and a 184-bp 3'-untranslated region. The ORF encodes a protein consisting of 483 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 14 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 34.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human OS-9 protein (SWISS-PROT Accession No. Q13438). Table 11 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human OS-9 protein (OS). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 27.8% in the N-terminal region of 281 amino acid residues. The positions of eight cysteines were conserved between the two proteins.

Table 11

HP MEEGGGGVRSLVPGGPVLLVLCGLLEASGGGRALPQLSDDIPFRVNWPGTEFSLPTTGVL 5 MAAETILSSLLGLLLL-GLLLPASLTGGVGSLNLEELSEMRYGIEILPLPVMGGQ OS HP YKEDNYVIMTTAHKEKYKCILP----LVTSGDEEEEKDYKGPNPRELLEPLFKQSSCSYR **... .*..*.* ** .. ***. .*.**. .***.*.* OS SQSSDVVIVSSKYKQRYECRLPAGAIHFQREREEETPAYQGPGIPELLSPM-RDAPCLLK HP IESYWTYEVCHGKHIRQYHEEKETGOKINIHEYYLGNMLAKNLLFEKEREAEEKEKSNEI*** *.*.*** * ... * .. 10 OS TKDWWTYEFCYGRHIQQYHME-DSEIKGEV--LYLG-----YYQSAFD----WDDET HP PTKNIEGOMTPYYPVGMGNGTPCSLKONRPRSSTVMYIC---HPESKHEILSVAEVTTCE*.. . ***. *.* ..***...* OS AKASKOHRLKRYHSOTYGNGSKCDL-NGRPREAEVRFLCDEGAGISGDYIDRVDEPLSCS HP YEVVILTPLLCSHPKYRFRASPV-NDIFCQ-SLPGSPFKPLTLRQLEQQEEILRVPFRRN 15 * ..* ** **.** * ..*.. ..*. ** ** . .. OS YVLTIRTPRLCPHPLLRPPPSAAPQAILCHPSLQPEEYMAYVQRQADSKQYGDKIIEELQ

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA313678) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03092> (SEQ ID NOS: 35, 45, and 55)

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Determination of the whole base sequence of the cDNA insert of clone HP03092 obtained from cDNA library of human liver revealed the structure consisting of a 19-bp 5'untranslated region, a 1824-bp ORF, and a 269-bp 3'untranslated region. The ORF encodes a protein consisting of

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607 amino acid residues and there existed at least six putative transmembrane domains. Figure 15 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the rat liver-specific transport protein (GenBank Accession No. L27651). Table 12 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat liver-specific transport protein (RN). Therein, the marks of — and * represent a gap and an amino acid residue identical with that of the protein of the present invention, respectively. The both proteins shared a homology of 70.0% in the entire region.

Table 12

	HP	MGFEELLEQVGGFGPFQLRNVALLALPRVLLPLHFLLPIFLAAVPAHRCALPGAPANFSH
		**** ** ********* * **** ** ***** * ****
5	RN	MGFEDILDKVGGFGPFQLRNLVLMALPRMLLPMHFILPVFMAAVPAHHCALPGAPANLSH
	HP	QDVWLEAHLPREPDGTLSSCLRFAYPQALPNTTLGEERQSRGELEDEPATVPCSQGWEYD
		** ****** ** ******** ** ** * * * * ****
	RN	QDLWLEAHLPRETDGSFSSCLRFAYPQTVPNVTLGTEVSNSGEPEGEPLTVPCSQGWEYD
	HP	HSEFSSTIATESQVGIYIIHLEVECRWRQSPWEAAGRGLPWEEAEAAGLGRDKVSYSPSW
10		*****
	RN	RSEFSSTIAT
	HP	RESLGGLLSGMEWDLVCEQKGLNRAASTFFFAGVLVGAVAFGYLSDRFGRRRLLLVAYVS
		***** * ** ** ****** *********
	RN	EWDLVCQQRGLNKITSTCFFIGVLVGAVVYGYLSDRFGRRRLLLVAYVS
15	HP	TLVLGLASAASVSYVMFAITRTLTGSALAGFTIIVMPLELEWLDVEHRTVAGVLSSTFWT
		**** *** * * * * * * ******** * **
	RN	SLVLGLMSAASINYIMFVVTRTLTGSALAGFTIIVLPLELEWLDVEHRTVAGVISTVFWS
	HP	GGVMLLALVGYLIRDWRWLLLAVTLPCAPGILSLWWVPESARWLLTQGHVKEAHRYLLHC
		*** ******* ****** **** *** * *********
20	RN	GGVLLLALVGYLIRSWRWLLLAATLPCVPGIISIWWVPESARWLLTQGRVEEAKKYLLSC
	HP	ARLNGRPVCEDSFSQEAVSKVAAGERVVRRPSYLDLFRTPRLRHISLCCVVVWFGVNFSY
		* ***** * * *** * * * * * * ****** * ****
		AKLNGRPVGEGSLSQEALNNVVTMERALQRPSYLDLFRTSQLRHISLCCMMVWFGVNFSY
	HP	YGLSLDVSGLGLNVYQTQLLFGAVELPSKLLVYLSVRYAGRRLTQAGTLLGTALAFGTRL
25		*** *****************
		YGLTLDVSGLGLNVYQTQLLFGAVELPSKIMVYFLVRRLGRRLTEAGMLLGAALTFGTSL
	HP	LVSSDMKSWSTVLAVMGKAFSEAAFTTAYLFTSELYPTVLRQTGMGLTALVGRLGGSLAP
		*** *** * * * *****************
		LVSLETKSWITALVVVGKAFSEAAFTTAYLFTSELYPTVLRQTGLGLTALMGRLGASLAR
30	HP	LAALLDGVWLSLPKLTYGGIALLAAGTALLLPETRQAQLPETIQDVERKSAPTSLQEEEM
		******* *** ***** ** ****** * ***
	RN	LAALLDGVWLLLPKVAYGGIALVAACTALLLPETKKAQLPETIQDVERKSTQEE
	HP	PMKQVQN
35	RN	DV

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI016020) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP03116> (SEQ ID NOS: 36, 46, and 56)

Determination of the whole base sequence of the cDNA insert of clone HP03116 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 32-bp 5'-untranslated region, a 945-bp ORF, and a 110-bp 3'-untranslated region. The ORF encodes a protein consisting of 314 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 16 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine at position 20. In addition, there exist in the amino acid sequence of this protein three sites at which Nglycosylation may occur (Asn-Arg-Thr at position 167, Asn-Asn-Ser at position 200 and Asn-Ile-Ser at position 273).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human Prostasin (SWISS-PROT Accession No. Q16651). Table 13 shows the comparison between amino acid sequences of the human protein of the present

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invention (HP) and the human Prostasin (PR). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.8% in the entire region.

Table 13

MGARGALLLALLLARAGLRKPESOEAAPLSGPCGRRVITSRIVGGEDAELGRWPW 10 HP ** *. ..** . .**.* *.** PR MAQKGVLGPGQLGAVAILLYLGLLRSGTG-AEGAEAPCG-VAPQARITGGSSAVAGQWPW HP QGSLRLWDSHVCGVSLLSHRWALTAAHCFETYSDLSDPSGWMVQFGQLTSMPSFWSLQAY . **** **.*.*.* *..*. PR QVSITYEGVHVCGGSLVSEQWVLSAAHCF---PSEHHKEAYEVKLGA-HQLDSY---SED 15 HP YTRYFVSNIYLSPRYLGNSPY-DIALVKLSAPVTYTKHIQPICLQASTFEFENRTDCWVT *.** ... ***..* *.*....*.*.*.. .* * .* ** PR AKVSTLKDIIPHPSYLQEGSQGDIALLQLSRPITFSRYIRPICLPAANASFPNGLHCTVT HP GWGYIKEDEALPSPHTLQEVQVAIINNSMCNHLF-LKYSFRKDIF--GDMVCAGNAQGGK 20 PR GWGHVAPSVSLLTPKPLQQLEVPLISRETCNCLYNIDAKPEEPHFVQEDMVCAGYVEGGK HP DACFGDSGGPLACNKNGLWYQIGVVSWGVGCGRPNRPGVYTNISHHFEWIQKLMAQSGMS *** ****** * **** * ****** * . . *** PR DACOGDSGGPLSCPVEGLWYLTGIVSWGDACGARNRPGVYTLASSYASWIQSKVTELQPR 25 HP QPDPSWPLLFFPLLWALPLLGPV PR VVPQTQESQPDSNLCGSHLAFSSAPAQGLLRPILFLPLGLALGLLSPWLSEH

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA159101) among ESTs. However, since they are partial sequences, it can not be judged whether or

not they encode the same protein as the protein of the present invention.

<HP10618> (SEQ ID NOS: 37, 47, and 57)

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Determination of the whole base sequence of the cDNA insert of clone HP10618 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 215-bp 5'-untranslated region, a 285-bp ORF, and a 1194-bp 3'-untranslated region. The ORF encodes a protein consisting of 94 amino acid residues and there existed a putative transmembrane domain at the N-terminus. Figure 17 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 9,709 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA287125) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

25 <HP10619> (SEQ ID NOS: 38, 48, and 58)

Determination of the whole base sequence of the cDNA insert of clone HP10619 obtained from cDNA library of the human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 11-bp 5'-untranslated region, a 657-bp ORF, and a 854-bp 3'-untranslated region. The ORF encodes a protein consisting of 218 amino acid residues and there existed a putative transmembrane domain at the N-terminus.

Figure 18 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. Z43089) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10622> (SEQ ID NOS: 39, 49, and 59)

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Determination of the whole base sequence of the cDNA insert of clone HP10622 obtained from cDNA library of the human liver revealed the structure consisting of a 43-bp 5'untranslated region, a 1383-bp ORF, and a 165-bp 3'untranslated region. The ORF encodes a protein consisting of 460 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 19 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 17. addition, there exist in the amino acid sequence of this protein four sites at which N-glycosylation may occur (Asn-Ser-Ser at position 23, Asn-Met-Ser at position 115, Asn-Glu-Thr at position 296 and Asn-Tyr-Thr at position 357).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human angiopoietin-1 (GenBank

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Accession No. U83508). Table 14 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human angiopoietin-1 (AN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 28.2% in the entire region and a homology of 39.1% in the C-terminal region of 215 amino acid residues.

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Table 14

HP **MFTIKLLLFIVPLVISS** 5 AN MTVFLSFAFLAAILTHIGCSNQRRSPENSGRRYNRIQHGQCAYTFILPEHDGNCRESTTD HP RIDQDNSSFDSLSPEPKSRFAMLDDVKILANGLLQLGHGLKDF-VHKTKGQINDIFQKLN AN QYNTNALQRDAPHVEPDFSSQKLQHLEHVMENYTQWLQKLENYIVENMKSEMAQI-OONA HP IFDQSFYDLSLQTSEIKEEEKELRR-TTYKLQVKNEEVKNMSLELNSKLESLLEEKILLO 10 *.. ** *. *. . ** *.. . AN VQNHTATMLEIGTSLLSQTAEQTRKLTDVETQVLNQTSRLEIQLLENSLSTYKLEKOLLO HP QKVKYLE-EQLTNLIQNQPETPEHPEVTSLKTFVEKQDNSIKDLLQTVEDQYKQLNQOHS *. . *.*... . * . ..*. . * ...* ...* AN QTNEILKIHEKNSLLEHKILEMEGKHKEELDTLKEEKEN-LOGLVTROTYIIOELEKOLN 15 HP QIKEIENQLRRTSIQEPTEISLSSKPRAPRTTPFLOLNEIRNVKHDGIPAECTTIYNRGE *.. . ***...*. * AN RATTNNSVLOKOOL-ELMDTVHNLVNLCTKEGVLL--KGGKREEEKPFR-DCADVYOAGF HP HTSGMYAIRPSN-SQVFHVYCDV-ISGSPWTLIQHRIDGSQNFNETWENYKYGFGRLDGE ..**.*. .* .. .*.*. .*. **.*** *** .*. .*. *** .** 20 AN NKSGIYTIYINNMPEPKKVFCNMDVNGGGWTVIOHREDGSLDFORGWKEYKMGFGNPSGE HP FWLGLEKIYSIVKQSNYVLRIELEDWKDNKHYIEY-SFYLGNHETNYTLHLVAITGNVPN AN YWLGNEFIFAITSORQYMLRIELMDWEGNRAYSOYDRFHIGNEKONYRLYLKGHTGTAGK HP AIP-ENKDLVFSTWDHKAKGHF-NCPEGYSGGWWWHDECGENNLNGKYNKPRAKSKPERR 25 .. *** **. .*** * .** .*** AN QSSLILHGADFSTKDADNDNCMCKCALMLTGGWWF-DACGPSNLNGMFY--TAGQNHGKL HP RGLSWKSONGRLYSIKSTKMLIHPTDSESFE .*..*. .*. **..**.* * AN NGIKWHYFKGPSYSLRSTTMMIRPLDF 30

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

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example, Accession No. R86161) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10625> (SEQ ID NOS: 40, 50, and 60)

Determination of the whole base sequence of the cDNA insert of clone HP10625 obtained from cDNA library of the human liver revealed the structure consisting of a 133-bp 5'-untranslated region, a 651-bp ORF, and a 465-bp 3'-untranslated region. The ORF encodes a protein consisting of 216 amino acid residues and there existed two putative transmembrane domains. Figure 20 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R59052) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP02883> (SEQ ID NOS: 61, 71, and 81)

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Determination of the whole base sequence of the cDNA insert of clone HP02883 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 191-bp 5'-untranslated region, a 1179-bp ORF, and a 2657-bp 3'-untranslated region. The ORF encodes a protein consisting of 392 amino acid residues and there existed three putative transmembrane domains. Figure 21 depicts the hydrophobicity/hydrophilicity profile, obtained

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by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 40 kDa that was almost identical with the molecular weight of 43,381 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar the Caenorhabditis to elegans hypothetical protein CET24F1.2 (GenBank Accession Z49912). Table 15 shows the comparison between amino acid sequences of the human protein of the present invention (HP) Caenorhabditis elegans hypothetical CET24F1.2 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.4% in the N-terminal region of 178 amino acid residues.

Table 15

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	HP	${\tt MEGVSALLARCPTAGLAGGLGVTACAAAGVLLYRIARRMKPTHTMVNCWFCNQDTLVPYG}$
		***. * * * * * * *
	CE	MEVAAAVGVIASVPILYK-AIRPR-IKTSVECWFCRKSTKVEYQ
	HP	${\tt NRNCWDCPHCEQYNGFQENGDYNKPIPAQYLEHLNHVVSSAPSLRDP-SQPQQ}$
25		.**** ****** *.******.* * * *
	CE	${\tt QRNSFTCPSCEQYNGFTEDGDYNRRIPGQAWTTPKRYCEPGKMQSEKPSTFLDRFGGVNM}$
	HP	${\tt WVSSQVLLCKRCNHHQTTKIKQLAAFAPREEGRYDEEVEVYRHHLEQMYKLCRPCQAAVE}$
		. ** **.* . .** .** .*.
	CE	${\tt SPKASNGLCSECNLGQEIIMNKVAEFEPIDEDRWNEELEDYRYKLERMYQLCPRCTIQVH}$
30	HP	${\tt YYIKHQNRQLRALLLSHQFKRREADQTHAQNFSSAVKSPVQVIILRALAFLACAFLLTTA}$
		****** *** ***
	CE	GKLEEDKKKY-SYLLKVKYKLKHAIGSTLREVMNNQKRSRRFFFAGGSTCEALHFGCLIS

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. F11409) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

10 <HP03140> (SEQ ID NOS: 62, 72, and 82)

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Determination of the whole base sequence of the cDNA insert of clone HP03140 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 29-bp 5'-untranslated region, a 1494-bp ORF, and a 972-bp 3'-untranslated region. The ORF encodes a protein consisting of 497 amino acid residues and there existed one putative transmembrane domain. Figure 22 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 51 kDa that was almost identical with the molecular weight of 54,245 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the Caenorhabditis elegans protein was similar to the CELC50D2 (GenBank Accession hypothetical protein AF040642). Table 16 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Caenorhabditis elegans hypothetical protein CELC50D2 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that

of the protein of the present invention, respectively. The both proteins shared a homology of 37.9% in the N-terminal region of 393 amino acid residues.

Table 16

HP MALWRGSAYAGFLALAVGCVFLLEPELPGSALRSLWSSLCLGPAPAPPGPVSPEGRLAAA MFSETFVPSIFSYKHRLLHLSVLFFIVPYWYSYYNDQHRLSSYSVETAMFLS CE HP WDALIVRPVRRWRRVAVGVNACVDVVLSGVKLLQALGLSPGNGKDHSILHSRNDLEEAFI 10 *. **.* * * **...******...* CE WERAIVKPGAMFKKAVIGFNCNVDLIVSGVRVVDALNTTCSEGKDQETLETLADLHQTFA HP HFMWKGAAAERFFSDKETFHDIAQVASEFPGAQHYVGGNAALIGQKFAAN-SDLKVLLCG **. .*****..*... *.*******.....*** .. .* * CE HFFORGAAAERYMSSEDOFNLLVAESEASTRSHHHIGGNAALMADRIAANFPSTEVYLVG 15 HP PVGPRLHELLDDNVFVPPESLQEVDEFHLILEYQAGEEWGQLKAPHANRFIFSHDLSNGA *.*** ..**. .* **.*.**** *. ** ..** **. CE PIGPRSQALLHPSVKRTNSTRILKDELHVILEYKQGEILGDWVAPSSSRFITSHDHFSGS HP MNMLEVFVSSLEEFQPDLVVLSGLHMMEGQSKELQRKRLLEVVTSISDIPTGIPVHLELA 20 CE MVVMEMFFKAIAOFRPDLVVITGVHLLEFOSKEMROEKMRLIKRNLLQIPPKVPIHLELG HP SMTNRELMSSIVHQQVFPAVTSLGLNEQELLFLTQSASGPH-SSLSSWNGVPDVGMVSDI CE SLAD-EIFSTDVINKILPYVDSLGINEQELTFLSHIANGPHMEEYPVQAGTVHVHKVVEM 25 HP LFWILKEHGR----SKSRASDLTRIHFHTLVYHILATVDGHWANQLAAVAAGARVAGT *.**** *.***... ...*.* *..**** CE LHWLLKTYGRDPTGQIASKTGYRLSRIHFHCLTYHIMVSSGTDWSNLAAGLAAGARIAGR HP QAC--ATETIDTSRVSLRAPQEFMTSHSEAGSRIVLNPNKPVVEWHREGISFHFTPVLVC ...*.*. ... *.*.*. 30 CE LSCNIGANTMDSELLEIRTPANFVLDKKIEKNYQFEAHKYMLTPFNIARCSTRLIRRKPP HP KDPIRTVGLGDAISAEGLFYSEVHPHY CE GGGILDEGVTFSDVHNVILNPTTRLPYPEEQLREHIEKTSSEIMKERNKIRYGTRKKKDS

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA356000) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10628> (SEQ ID NOS: 63, 73, and 83)

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Determination of the whole base sequence of the cDNA insert of clone HP10628 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 66-bp 5'-untranslated region, a 1254-bp ORF, and a 297-bp 3'-untranslated region. The ORF encodes a protein consisting of 417 amino acid residues and there existed four putative transmembrane domains. Figure 23 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 46 kDa that was almost identical with the molecular weight of 45,461 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Schistosoma mansoni ATP-cassette family protein (GenBank Accession No. L26286). Table 17 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Schistosoma mansoni ATP-cassette family protein (SM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The

both proteins shared a homology of 39.5% in the C-terminal region of 294 amino acid residues.

Table 17

5 HP MLVHLFRVGIRGGPFPGRLLPPLRFQTFSAVRYSDGYRSSSLLRAVAHLRSQLWAHLPRA SM MFSALCRRGFLTNKVSQFRSTYKCDHYNLKT HP PLAPRWSPSAWCWVGGALLGPMVLSKHPHLCLVALCEAEEAPPASSTPHVVGSRFNWKLF SM HIKPLKCSSSLRLTVGTGLFIALHSKISPESRIOTVOCEVDSYQTDQITFAKSGGIPRYI 10 HP WQFLHPHLLVLGVAVVLALGAALVNVQIPLILGQLVEVVAKYTRDHVGSFMTESQNLSTH .. *. . * *.. *. **..** *** **..*.* * *... SM GVLILPDCVYLFGAILGAFVAAVMNVYIPLYLGDFVSSLSRCVVTHEG-FVSAVYVPTLR HP LLILYGVQGLLTFGYLVLLSHVGERMAVDMRRALFSSLLRYCQPQGAELGQDITFFDANK * .*.* ** *. **. ***** ** .**..*. * SM LCSSYLLQSLSTFLYIGLLGSVGERMARRMRIQLFRKLV-Y-----QDVAYFDVHS 15 HP TGQLVSRLTTDVQEFKSSFKLVISQGLRSCTQVAGCLVSLSMLSTRLTLLLMVATPALMG SM SGKLVEIIGSDVQNFKSSFKQCISQGLRNGIQVVGSVFALLSISPTLTAALIGCLPCVFL HP VGTLMGSGLRKLSCQCQEQIARAMGVADEALGNVRTVRAFAMEQREEERYGAELEACRCR 20 .*.***..**..* . *.* . .. ***...***...***. SM IGSLMGTELRHISREVQSQNSLFASLIDEAFSHIRTVKSLAMEDFLINKINYNVDKAKML HP AEELGRGIALFQGLSNIAFNCMVLGTLFIGGSLVAGQQLTGGDLMSFLVASQTVQRL ,*.*. **. ******...* <u>.</u>***.*.*..*.*****...** SM SEKLSFGIGSFQGLSNLTLNGVVLGVLYVGGHLMSRGELDAGHLMSFLATTQTLQRSLTQ 25

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. U66688) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present inv ntion.

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<HP10629> (SEQ ID NOS: 64, 74, and 84)

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Determination of the whole base sequence of the cDNA insert of clone HP10629 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 259-bp 5'-untranslated region, a 1950-bp ORF, and a 1060-bp 3'-untranslated region. The ORF encodes a protein consisting of 649 amino acid residues and there existed at least eight putative transmembrane domains. Figure 24 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis hypothetical protein CELF38B6 (GenBank Accession No. U40060). Table 18 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Caenorhabditis elegans hypothetical protein CELF38B6 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.1% in the C-terminal region of 445 amino acid residues.

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Table 18

•	HP	MIPNQHNAGAGSHQPAVFRMAVLDTDLDHILPSSVLPPFWAKLVVGSVAIVCFARSYDGD
	CE	MKYAEINVNSGKHFRLNYKLHETS
5	HP	FVFDDSEAIVNNKVAGVVGRADLLCALFFLLSFLGYCKAFRESNKEGAHSSTFWVLLSIF
	CE	${\tt TLGYHVVNIICHTVATLVFYKLGKQLEHIFDFFNIAFSASILFAVHPVHTEAVANITGRA}$
	HP	${\tt LGAVAMLCKEQGITVLGLNAVFDILVIGKFNVLEIVQKVLHKDKSLENLGMLRNGGLLFR}$
	CE	ELLMTIFSLAALILHVKNREINCKFVLLVILSTLSKEQGLMTIPIAICIDFLAHRSCRSN
	HP	MTLLTSGGAGMLYVRWRIMGTGPPAFTEVDNPASFADSMLVRAVNYNYYYSLNAWLLLCP
10		* * *** .* * *
	CE	FVRMICLLVAIGFLRMMVNGFEAAKFTKLDNPTAFLNSKFYRMINYTYIWLYHAYLLVIP
	HP	WWLCFDWSMGCIPLIKSISDWRVIALAALWFCLIGLICQALCSEDGHKRRILTLGLGFLV
		****.**** * * . * . * . *
	CE	VNLCFDYSMGCISSITTMWDLRALSPVLIFTIVIIGVKFQNECRAFTLSSLMGI
15	HP	IPFLPASNLFFRVGFVVAERVLYLPSIGYCVLLTFGFGALSKHTKKKKLIAAVVLGILFI
		*.*****.** *** .******* *.* * ** * **
	CE	ISFLPASNIFFTVGFSIAERVLYLPSAGFCLLCAIIFKKLSVHFKNADVLSITLILLLIS
	HP	NTLRCVLRSGEWRSEEQLFRSALSVCPLNAKVHYNIGKNLADKGNQTAAIRYYREAVRLN
		.* * ****** **.**** ***.** *.*.** . **
20	CE	KTYRRSGEWKTELSLYSSGLSVCPTNAKIHYNLGKVLGDNGLTKDAEKNYWNAIKLD
	HP	PKYVHAMNNLGNILKERNELQEAEELLSLAVQIQPDFAAAWMNLGIVQNSLKRFEAAEQS
		. .*.***** ***.** .**.*** * .**.*
	CE	PSYEQALNNLGNLLEKSGDSKTAESLLARAVTLRPSFAVAWMNLGISQMNLKKYYEAEKS
	HP	YRTAIKHRRKYPDCYYNLGRLYADLNRHVDALNAWRNATVLKPEHSLAWNNMIILLDNTG
25		* *** *** **. **. *****.** .*.*
	CE	LKNSLLIRPNSAHCLFNLGVLYQRTNRDEMAMSAWKNATRIDPSHSQSWTNLFVVLDHLS
	HP	NLAQAEAVGREALELIPNDHSLMFSLANVLGKSQKYKESEALFLKAIKANPNAASYHGNL

	CE	QCSQVIDLSYQALSSVPNESRVHMQIGSCHAKHSNFTAAENHIKSAIDLNPTSVLFHANL
30	HP	AVLYHRWGHLDLAKKHYEISLQLDPTASGTKENYGLLRRKLELMQKKAV
		.* ** * *.
	CE	GILYQRMSRHKEAESQYRIVLALDSKNIVAKQNLQKLEEHNCYNSTLP

sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA450191) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10635> (SEQ ID NOS: 65, 75, and 85)

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Determination of the whole base sequence of the cDNA insert of clone HP10635 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 65-bp 5'-untranslated region, a 282-bp ORF, and a 111-bp 3'-untranslated region. The ORF encodes a protein consisting of 93 amino acid residues and there existed two putative transmembrane domains. Figure 25 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 9,489 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA516481) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10636> (SEQ ID NOS: 66, 76, and 86)

Determination of the whole base sequence of the cDNA insert of clone HP10636 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure

consisting of a 179-bp 5'-untranslated region, a 1278-bp ORF, and a 255-bp 3'-untranslated region. The ORF encodes a protein consisting of 425 amino acid residues and there existed ten putative transmembrane domains. Figure 26 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. Z43270) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10640> (SEQ ID NOS: 67, 77, and 87)

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Determination of the whole base sequence of the cDNA insert of clone HP10640 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 52-bp 5'-untranslated region, a 450-bp ORF, and a 553-bp 3'-untranslated region. The ORF encodes a protein consisting of 149 amino acid residues and there existed at least two putative transmembrane domains. Figure 27 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 17 kDa that was almost identical with the molecular weight of 16,829 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana hypothetical

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protein F27F23.14 (GenBank Accession No. AC003058). Table 19 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Arabidopsis thaliana hypothetical protein F27F23.14 (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 46.5% in the entire region other than the N-terminal region.

Table 19

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N34717) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

Determination of the whole base sequence of the cDNA insert of clone HP10644 obtained from cDNA library of the human retinoblastoma cell line WERI-RB revealed the structure consisting of a 221-bp 5'-untranslated region, a 1191-bp ORF, and a 204-bp 3'-untranslated region. The ORF encodes a protein consisting of 396 amino acid residues and there existed two putative transmembrane domains. Figure 28 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar the Caenorhabiditis to elegans hypothetical protein B0511.8 (GenBank Accession No. AF067608). Table 20 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Caenorhabiditis elegans hypothetical protein B0511.8 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 31.3% in the region of 361 amino acid residues other than the N-terminal region and the C-terminal region.

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Table 20

	HS	MAMIELGFGRQNFHPLKRKSSLLLKL
	CE	CDKNGQYLSVQEEIDAENKVQRKIAPGLNEKVLERVTQMLMKQEKSTETYMIWLKNLRVP
5	HS	IAVVFAVLLFCEFLIYYLAIFQCNWPEVKTTASDGEQTTREPVLKAMFLADTHLLGEFLG
		* * * *. *. *. *. *. *. *. *. *.
	CE	ILLAIILVVYNEYFIFFIAFSSCQWPCKYGRCS-ESSVKAFMISDTHLLGKING
	HS	HWLDKLRREWQMERAFQTALWLLQPEVVFILGDIFDEGKWSTPEAWADDVERFQKMFRHP
		****** .** * *. *.**************
10	CE	HWLDKLKREWQMYQSFWISTWIHSPDVTFFLGDLMDEGKWAGRPVFEAYAERFKKLFG
	HS	SHVQLKVVAGNHDIGFHYEMNTYKVERFEKVFSSERLFSWKGINFVMVNSVALNGDGCGI
	CE	DNEKVITLAGNHDLGFHYALVQTFATHLTPTVELKNYLLIMPETLEMFKKEFRR
	HS	CSETEAELIEVSHRLNCSREARG-SSR-CGPGPLLPTSAPVLLQHYPLYRRS
15		.* * ** * . * * *
	CE	GLIDEMKIKKHRFVLINSMAMHGDGCRLCHEAELILEKIKSRNPKNRPIVLQHFPLYRKS
	HS	DANCSGEDAAPAEERDIPFKENYDVLSREASQKLLWWLQPRLVLSGHTHSACEVH
		**.*. *
	CE	DAECDQVDEQHEIDLKEMYREQWDTLSKESSLQIIDSLNPKAVFGGHTHKMCKKKWNKTG
20	HS	HGGRVPELSVPSFSWRNRNNPSFIMGSITPTDYTLSKCYLPREDVVLIIYC-GVVGFLVV
		* .* ****** . * **.* **.* *
	CE	NSEYFYEYTVNSFSWRNGDVPAMLLVVIDGDNVLVSSCRLPSEILQIMVYIFGGIGILAK
	HS	LTLTHFGLLASPFLSGLNLLGKRKTR
		•
25	CE	MYNDLITPAPLEWNVNNIAVCTAILLVMIINVVALIFTIFWCLRSKDEGGEIDSNGVVIN

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R88381) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10656> (SEQ ID NOS: 69, 79, and 89)

Determination of the whole base sequence of the cDNA insert of clone HP10656 obtained from cDNA library of the human lymphoma cell line U937 revealed the consisting of a 68-bp 5'-untranslated region, a 1053-bp ORF, and a 739-bp 3'-untranslated region. The ORF encodes a protein consisting of 350 amino acid residues and there existed two putative transmembrane domains. Figure 29 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 41 kDa that was almost identical with the molecular weight of 40,043 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 54 kDa to which sugar chains are presumably attached. In addition, there exist in the amino acid sequence of this protein four sites at which N-glycosylation may occur (Asn-Cys-Thr at position 148, Asn-Tyr-Thr at position 155, Asn-Gln-Thr at position 162 and Asn-Lys-Ser at position 190).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA917816) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

30 <HP10672> (SEQ ID NOS: 70, 80, and 90)

Determination of the whole base sequence of the cDNA insert of clone HP10672 obtained from cDNA library of the

human thymus revealed the structure consisting of a 244-bp 5'-untranslated region, a 462-bp ORF, and a 77-bp 3'-untranslated region. The ORF encodes a protein consisting of 153 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 30 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. When expressed in COS cells, a product of 17 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N48700) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03194> (SEQ ID NOS: 91, 101, and 111)

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Determination of the whole base sequence of the cDNA insert of clone HP03194 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 120-bp 5'-untranslated region, a 912-bp ORF, and a 2406-bp 3'-untranslated region. The ORF encodes a protein consisting of 303 amino acid residues and there existed four putative transmembrane domains. Figure 31 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the

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protein was similar to the mouse hyperpolarization-activated cation channel HAC3 (GenBank Accession No. AJ225124). Table 21 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the mouse hyperpolarization-activated cation channel HAC3 (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 92.5% in the N-terminal region of 293 amino acid residues.

Table 21

HS MEAEQRPAAGASEGATPGLEAVPPVAPPPATAASGPIPKSGPEPKRRHLGTLLQPTVNKF 15 ************** MM MEEEARPAAGAGEAATPARET-PPAAPAOARAASGGVPESAPEPKRRQLGTLLQPTVNKF HS SLRVFGSHKAVEIEQERVKSAGAWIIHPYSDFRFYWDLIMLLLMVGNLIVLPVGITFFKE *********** 20 MM SLRVFGSHKAVEIEOERVKSAGAWIIHPYSDFRFYWDLIMLILMVGNLIVLPVGITFFKE HS ENSPPWIVFNVLSDTFFLLDLVLNFRTGIVVEEGAEILLAPRAIRTRYLRTWFLVDLISS MM ENSPPWIVFNVLSDTFFLLDLVLNFRTGIVVEEGAEILLAPRAIRTRYLRTWFLVDLISS HS IPVDYIFLVVELEPRLDAEVYKTARALRIVRFTKILSLIRLIRLSRLIRYIHQWEEIFHM 25 *********** MM IPVDYIFLVVELEPRLDAEVYKTARALRIVRFTKILSLLRLLRLSRLIRYIHOWEEIFHM HS TYDLASAVVRIFNLIGMMLLLCHWDGCLQFLVPMLQDFPPDCWVSINHMVVRSPHSSAFP *************** MM TYDLASAVVRIFNLIGMMLLLCHWDGCLQFLVPMLQDFPSDCWVSMNRMVNHSWGRQYSH 30 HS GPS MM ALFKAMSHMLCIGYGQQAPVGMPDVWLTMLSMIVGATCYAMFIGHATALIQSLDSSRRQY

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AI571225) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03219> (SEQ ID NOS: 92, 102, and 112)

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Determination of the whole base sequence of the cDNA insert of clone HP03219 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 55-bp 5'-untranslated region, a 852-bp ORF, and a 237-bp 3'-untranslated region. The ORF encodes a protein consisting of 283 amino acid residues and there existed four putative transmembrane domains. Figure 32 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human putative membrane protein 54TMp (GenBank Accession No. AF004876). Table 22 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the human putative membrane protein 54TMp (TM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 56.5% in the entire region.

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Table 22

MADPHQLFDDTSSAQSRGYGAQRAPGGLSYPAASPT-PHAAF HS ** * * * * * * * 5 TM MAYHSGYGAHGSKHRARAAPDPPPLFDDT----SGGYSSQ--PGGYPATGADVAFSVNHL HS LADPVSNMAMAYGSSLAAQGKELVDKNIDRFIPITKLKYYFAVDTMYVGRKLGLLFFPYL TM LGDPMANVAMAYGSSIASHGKDMVHKELHRFVSVSKLKYFFAVDTAYVAKKLGLLVFPYT 10 HS HODWEVOYQODTPVAPRFDVNAPDLYIPAMAFITYVLVAGLALGTQDRFSPDLLGLQASS TM HQNWEVQYSRDAPLPPRQDLNAPDLYIPTKAFITYVLLAGMALGIQKRFSPEVLGLCAST HS ALAWLTLEVLAILLSLYLVTVNTDLTTIDLVAFLGYKYVGMIGGVLMGLLFGKIGYYLVL **.*...***.**.**.**.**.**.**.* 15 TM ALVWVVMEVLALLLGLYLATVRSDLSTFHLLAYSGYKYVGMILSVLTGLLFGSDGYYVAL HS GWCCVAIFVFMIRTLRLKILADAAAEGVPVRGARNOLRMYLTMAVAAAQPMLMYWLTFHL TM AWTSSALMYFIVRSLRTAAL-GPDSMGGPV--PRORLOLYLTLGAAAFQPLIIYWLTFHL HS VR 20 ** TM VR

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H86659) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03236> (SEQ ID NOS: 93, 103, and 113)

Determination of the whole base sequence of the cDNA insert of clone HP03236 obtained from cDNA library of human

fibrosarcoma cell line HT-1080 revealed the structure consisting of a 252-bp 5'-untranslated region, a 1467-bp ORF, and a 620-bp 3'-untranslated region. The ORF encodes a protein consisting of 488 amino acid residues and there existed seven putative transmembrane domains. Figure 33 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the Caenorhabditis was similar the to hypothetical protein ZC513.5 (GenBank Accession No. U53155). Table 23 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Caenorhabditis elegans hypothetical protein ZC513.5 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.5% in the intermediate region of 365 amino acid residues.

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Table 23

HS MAGKGSSGRRPLLLGLLVAVATVHLVICPYTKVEESFNLQATHDLLYHWQDLEQYDHLEF .*** .* 5 CE MKMKYDHSQF HS PGVVPRTFLGPVVIAVFSSPAVYVLSLLEMSKFYSQLIVRGVLGLGVIFGLWTLQKEVRR ******* **. .*..*** *..*.. *..** CE PGVVPRTFIGPISLAILSSPMSFIFRFWAIPKMWOLLLIRATLGLMNAMAFLYFARSVNR HS HFGAMVATMFCWVTAMOFHLMFYCTRTLPNVLALPVVLLALAAWLRHEWARFIWLSAFAI 10 CE KFGRETAMYLRLIMCTQFHYIFYMSRPLPNTFALILVMIVFERLLEGRYESAVRYATASV HS IVFRVELCLFLGLILL--LALGNRKV-SVVRALRHAVPAGILCLGLTVAVDSYFWRQLTW *.** ** *. * ..* . *. ** . *. .*. * CE ILFRCELVLLYGPIFLGYMISGRLKVFGFDGAIAIGVRIAAMCLAVSIPIDSYFWGRPLW 15 HS PEGKVLWYNTVLNKSSNWGTSPLLWYFYSALPRGLGCSLLFIPLG-LVDRRTHAPTVLAL ***.*...*.* *.* *.** *.******* * . *..*** **** CE PEGEVMFFNVVENRSHEYGTOPFLWYFYSALPRCLLTTTLLVPLGLLVDRRLPOIVLPSV HS GFMALYSLLPHKELRFIIYAFPMLNITAARGCSYLLNNYKKSWLYKAGSLLVIGHLVVNA 20 CE IFIFLYSFLPHKELRFIIYVLPIFCLSAAVFCARMLINRHKSFFRMILFFGVILHLLANV HS AYSATALYVSHFNYPGGVAMO--RLHOLVPPOTDVLLHIDVAAAQTGVSRFLQVNSAWRY ... * ..** * *****.***.* ... * *. **** *.. ... CE LCTGMFLLVASKNYPGFDALNYLQFQNRFDAKKPVTVYIDNACAQTGVNRFLHINDAWT

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA744858) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03237> (SEQ ID NOS: 94, 104, and 114)

Determination of the whole base sequence of the cDNA insert of clone HP03237 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 101-bp 5'-untranslated region, a 549-bp ORF, and a 1106-bp 3'-untranslated region. The ORF encodes a protein consisting of 182 amino acid residues and there existed four putative transmembrane domains. Figure 34 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human intestinal membrane A4 protein (SWISS-PROT Accession No. Q04941). Table 24 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the human intestinal membrane A4 protein (IM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 32.4% in the intermediate region of 111 amino acid residues.

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Table 24

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R14227) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03267> (SEQ ID NOS: 95, 105, and 115)

Determination of the whole base sequence of the cDNA insert of clone HP03267 obtained from cDNA library of human liver revealed the structure consisting of a 148-bp 5'untranslated region, a 555-bp ORF, and a 715-bp 3'untranslated region. The ORF encodes a protein consisting of 184 amino acid residues and there existed two putative transmembrane domains. Figure 35 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 21 kDa that was almost id ntical with the molecular

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weight of 20,733 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human polyposis locus protein 1 (SWISS-PROT Accession No. Q00765). Table 25 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the human polyposis locus protein 1 (PL). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 59.1% in the entire region.

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Table 25

HS MDGLRQRVEHFLEQRNLVTEVLGALEAKTGVEKRYLAAGAVTLLSLYLLFGYGASLLCNL

PL MRERFDRFLHEKNCMTDLLAKLEAKTGVNRSFIALGVIGLVALYLVFGYGASLLCNL
HS IGFVYPAYASIKAIESPSKDDDTVWLTYWVVYALFGLAEFFSDLLLSWFPFYYVGKCAFL

PL IGFGYPAYISIKAIESPNKEDDTQWLTYWVVYGVFSIAEFFSDIFLSWFPFYYMLKCGFL

HS LFCMAPRPWNGALMLYQRVVRPLFLRHHGAVDRIMNDLSGRALDAAAGITRNVKPSQTPQ

25 PL LWCMAPSPSNGAELLYKRIIRPFFLKHESQMDSVVKDLKDKSKETADAITKEAKKATVNL HS PKDK

PL LGEEKKST

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or mor (for

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example, Accession No. R09702) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP03270> (SEQ ID NOS: 96, 106, and 116)

Determination of the whole base sequence of the cDNA insert of clone HP03270 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 132-bp 5'-untranslated region, a 423-bp ORF, and a 656-bp 3'-untranslated region. The ORF encodes a protein consisting of 140 amino acid residues and there existed four putative transmembrane domains. Figure 36 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 17 kDa that was somewhat larger than the molecular weight of 15,864 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Schizosaccharomyces pombe hypothetical protein (EMBL Accession No. AL031854). Table 26 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Schizosaccharomyces pombe hypothetical protein (SP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.4% in the entire region.

PCT/JP99/06412

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Table 26

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T30721) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03298> (SEQ ID NOS: 97, 107, and 117)

Determination of the whole base sequence of the cDNA insert of clone HP03298 obtained from cDNA library of human lymphoma cell line U937 revealed the structure consisting of a 182-bp 5'-untranslated region, a 462-bp ORF, and a 455-bp 3'-untranslated region. The ORF encodes a protein consisting of 153 amino acid residues and there existed at least one putative transmembrane domain. Figure 37 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 17.5 kDa that was almost identical with the molecular

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weight of 17,360 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Schizosaccharomyces SPBC119.09c (EMBL Accession hypothetical protein AL022117). Table 27 shows the comparison between amino acid sequences of the human protein of the present invention (HS) and the Schizosaccharomyces pombe hypothetical protein SPBC119.09c (SP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 41.9% in the entire region other than the N-terminal region.

Table 27

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA043039) among ESTs. However, since

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they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

5 <HP10631> (SEQ ID NOS: 98, 108, and 118)

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Determination of the whole base sequence of the cDNA insert of clone HP10631 obtained from cDNA library of the human retinoblastoma cell line WERI-RB revealed the structure consisting of a 226-bp 5'-untranslated region, a 522-bp ORF, and a 2741-bp 3'-untranslated region. The ORF encodes a protein consisting of 173 amino acid residues and there existed one putative transmembrane domain. Figure 38 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W26443) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10658> (SEQ ID NOS: 99, 109, and 119)

Determination of the whole base sequence of the cDNA insert of clone HP10658 obtained from cDNA library of the human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 24-bp 5'-untranslated region, a 228-bp ORF, and a 679-bp 3'-untranslated region. The ORF encodes a protein consisting of 75 amino acid residues and there existed two putative transmembrane domains. Figure 39 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In

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vitro translation resulted in formation of a translation product of 14 kDa or less that was almost identical with the molecular weight of 8,625 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T85006) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10663> (SEQ ID NOS: 100, 110, and 120)

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Determination of the whole base sequence of the cDNA insert of clone HP10663 obtained from cDNA library of the human lymphoma cell line U937 revealed the structure consisting of a 67-bp 5'-untranslated region, a 480-bp ORF, and a 576-bp 3'-untranslated region. The ORF encodes a protein consisting of 159 amino acid residues and there existed two putative transmembrane domains. Figure 40 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA336522) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

30 <HP03165> (SEQ ID NOS: 121, 131, and 141)

Determination of the whole base sequence of the cDNA insert of clone HP03165 obtained from cDNA library of human

epidermoid carcinoma cell line KB revealed the structure consisting of a 128-bp 5'-untranslated region, a 1911-bp ORF, and a 1195-bp 3'-untranslated region. The ORF encodes a protein consisting of 636 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 41 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 61 kDa that was smaller than the molecular weight of 72,033 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 33.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human β -galactosidase (GenBank Protein ID No. AAA51822). Table 28 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human β -galactosidase (GL). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.8% in the entire region.

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Table 28

	HP	${\tt MTTWSLRRRPARTLGLLLLVVLGFLVLRRLDWSTLVPLRLRHRQLGLQAKGWNFMLEDST}$
		.** .* .*
5	GL	MPGFLVRILPLLLVLLLLGPTRGLRNATQRMFEIDYSRDSFLKDGQP
	HP	${\tt FWIFGGSIHYFRVPREYWRDRLLKMKACGLNTLTTYVPWNLHEPERGKFDFSGNLDLEAF}$
		***** *** **.***** ** *****.*** .** *.*
	GL	${\tt FRYISGSIHYSRVPRFYWKDRLLKMKMAGLNAIQTYVPWNFHEPWPGQYQFSEDHDVEYF}$
	HP	${\tt VLMAAEIGLWVILRPGPYICSEMDLGGLPSWLLQDPGMRLRTTYKGFTEAVDLYFDHLMS}$
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	GL	${\tt LRLAHELGLLVILRPGPYICAEWEMGGLPAWILLEKESILLRSSDPDYLAAVDKWLGVLLP}$
	HP	RVVPLQYKRGGPIIAVQVENEYGSY-NKDPAYMPYVKKALEDRGIVELLLTSDNKDG
		** ***.*.******* . * .**
	GL	${\tt KMKPLLYQNGGPVITVQVENEYGSYFACDFDYLAFLQKRFRHHLGDDVVLFTTDGAHKTF}$
15	HP	${\tt LSKGIVQGVLATINLQSTHELQLLTTFLFNVQGTQPKMVMEYWTGWFDSWGGPHNILD}$
		*. * .**. *
	GL	${\tt LKCGALQGLYTTVDFGTGSNITDAFLSQRKCEPKGPLINSEFYTGWLDHWGQPHSTIK}$
	HP	${\tt SSEVLKTVSAIVDAGSSINLYMFHGGTNFGFMNGAMHFHDYKSDVTSYDYDAVLTEAGDY}$
		** * ***** ***** * ******
20	GL	TEAVASSLYDILARGASVNLYMFIGGTNFAYWNGANSPYAAQPTSYDYDAPLSEAGDL
	HP	TAKYMKLRDFFGSISGIPLPPPPDLLPKMPYEPLTPVLYLSLWDALKYLGEPIKSEKPIN
		*.**. *** * * * ***
	GL	TEKYFALRNIIQKFEKVPEGPIPPSTPKFAYGKVTLEKLKTVGAALDILC-PSGPIKS
	HP	MENLPVNGGNGQSFGYILYETSITSSGILSGHVHDRGQVFVNTVSIGFLDYKT
25		. * * .*. * * * * * *
	GL	LYPLTFIQVK-QHYGFVLYRTTLPQDCSNPAPLSSPLNGVHDRAYVAVDGIPQGVLE-RN
	HP	TKIAVPLI-QGYTVLRILVENRGRVNYGENIDDQRKGLIGNLYLNDSPLKNFRIYSL
		. *
	GL	NVITLNITGKAGATLDLLVENMGRVNYGAYIND-FKGLVSNLTLSSNILTDWTIFPLDTE
30	HP	DMKKSFFQRFGLDKWSSLPETPTLPAFFLGSLSISSTPCDTFLKLEGWE
		* .** *****. * * *** **.
	GL	DAVRSHLGGWGHRDSGHHDEAWAHNSSNYTLPAFYMGNFSIPSGIPDLPQDTFIQFPGWT
	HP	KGVVFINGQNLGRYW-NIGPQKTLYLPGP-WLSSGINQVIVFEETMAGPALQFTETPHLG
		** *.*** ***** . *** ****. **.
35	GL	KGQVWINGFNLGRYWPARGPQLTLFVPQHILMTSAPNTITVLELEWAPCSSDDPELCAVT

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HP RNQYIK

GL FVDRPVIGSSVTYDHPSKPVEKRLMPPPPQKNKDSWLDHV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA054017) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP03266> (SEQ ID NOS: 122, 132, and 142)

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Determination of the whole base sequence of the cDNA insert of clone HP03266 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 69-bp 5'-untranslated region, a 957-bp ORF, and a 1464-bp 3'-untranslated region. The ORF encodes a protein consisting of 318 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 42 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 34 kDa that was almost identical with the molecular weight of 35,363 predicted from the ORF.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana putative ribotol dehydrogenase (GenBank Protein ID No. AAC23625). Table 29 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the

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Arabidopsis thaliana putative ribotol dehydrogenase (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.0% in the region of 483 residues other than the N-terminal region.

Table 29

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10 HP MVELMFPLLLLLLPFILYMAAPQIRKMLSSGVCTSTVQLPGKVVVVTGANTGIGKETAKE**...*** *.*. ΑT MGIYGVMTGKKGKSGFGSASTAEDVTQAIDASHLTAIITGGTSGIGLEAARV HP LAQRGARVYLACRDVEKGELVAKEIQTTTGNQQVLVRKLDLSDTKSIRAFAKGFLAEEKH . * . *..* ..*.*.**.*. *** . . . 15 AT LAMRGAHVIIAARNPKAANESKEMILOMNPNARVDYLQIDVSSIKSVRSFVDQFLALNVP HP LHVLINNAGVMMCPYSKTADGFEMHIGVNHLGHFLLTHLLLEKLK----ESAPSRIVNV *..*******.**.. *.**.***.*****.** AT LNILINNAGVMFCPFKLTEDGIESQFATNHIGHFLLTNLLLDKMKSTARESGVQGRIVNL 20 HP SSLAH---HLGRIHFHNLQGEKFYNAGLAYCHSKLANILFTQELARRLKGSG--VTTYSV *.. ** ***:*: * ... * ... * ... * ** . . *.*.... AT SSIAHTYTYSEGIKFQGINDPAGYSERRAYGOSKLSNLLHSNALSRRLOEEGVNITINSV HP HPGTVQSELVRHSSFMRWMWWLFSF-FIKTPQQGAQTSLHCALTEGLEILSGNHFSDCHV *** * ..* *.*.** * *. .**.*. . ** ..*. ..*... 25 AT HPGLVTTNLFRYSGFSMKVFRAMTFLFWKNIPQGAATTCYVALHPDLEGVTGKYFGDCNI HP AWVSAQARNETIARRLWDVSCDLLGLPID . * * * . . * . * * * . . AT VAPSKFATNNSLADKLWDFSVFLIDSISK

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shar d a homology of 90% or more (for example, Accession No. D17020) among ESTs. How ver, since

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they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

5 <HP03287> (SEQ ID NOS: 123, 133, and 143)

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Determination of the whole base sequence of the cDNA insert of clone HP03287 obtained from cDNA library of human thymus revealed the structure consisting of a 83-bp 5'untranslated region, a 249-bp ORF, and a 1133-bp 3'untranslated region. The ORF encodes a protein consisting of 82 amino acid residues and there existed one putative transmembrane domain at the N-terminus and one at the Cterminus, respectively. Figure 43 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Schizosaccharomyces pombe hypothetical protein 9.0kDa (SWISS-PROT Accession 013825). Table 30 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Schizosaccharomyces pombe hypothetical protein 9.0kDa (SP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 45.7% in the entire region.

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SP RTVMTFPLIAINTIVIVYNLVLG

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Table 30

HP MAFTLYSLLQAALLCVNAIAVLHEERFLKNIGWGTDQGIGGFGE-EPGIKSQLMNLIRSV

... .** .** .*** .*** .*** .***.

SP MFGFGNILYVTLLLLNAVAILSEDRFLGRIGWSQSAAL-GFGDRQDTIKSRILHLIRAI

HP RTVMRVPLIIVNSIAIVLLLLFG

**** *** .*.*.** *..*

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA853098) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10665> (SEQ ID NOS: 124, 134, and 144)

Determination of the whole base sequence of the cDNA insert of clone HP10665 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 31-bp 5'-untranslated region, a 744-bp ORF, and a 142-bp 3'-untranslated region. The ORF encodes a protein consisting of 247 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 44 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 28 kDa that was somewhat larger than the molecular weight of 25,320 predicted from the ORF. In this case, the addition of a microsome led to the formation

of a product of 27 kDa. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from aspertic acid at position 26.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA055367) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10669> (SEQ ID NOS: 125, 135, and 145)

Determination of the whole base sequence of the cDNA insert of clone HP10669 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 73-bp 5'-untranslated region, a 621-bp ORF, and a 612-bp 3'-untranslated region. The ORF encodes a protein consisting of 206 amino acid residues and there existed one putative transmembrane domain. Figure 45 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AF086533) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10670> (SEQ ID NOS: 126, 136, and 146)

Determination of the whole base sequence of the cDNA

insert of clone HP10670 obtained from cDNA library of human retinoblastoma cell line WERI-RB revealed the structure consisting of a 117-bp 5'-untranslated region, a 1299-bp ORF, and a 606-bp 3'-untranslated region. The ORF encodes a protein consisting of 432 amino acid residues and there existed seven putative transmembrane domains. Figure 46 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis hypothetical protein CELM03F8.2 (GenBank Protein ID No. AAB65910). Table 31 shows the comparison between amino acid sequences of the human protein of the present invention (HP) Caenorhabditis elegans hypothetical CELM03F8.2 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 39.6% in the N-terminal region of 376 residues.

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Table 31

HP MDARWWAVVVLAAFPSLGAGGETPEAPPESWTQLWFFRFVVNAAGYASFMVPGYLLVQYF **. . .* .*. . **.. .*. .*. * 5 CE MDRSIMPIDSPARDKPPD--ELVWPLRLFLILLGYSTVATPAAILIYYV HP RRKNYLETGRGLCFPLVKACVFGNEPKASDEVPLA---PRTEAAETTPMW-----QALKL .*.*..... CE RRNRHAFETPYLSIRLLLRS-FAVGNPEYOLIPTGEKOARKENDSIPOTRAOCINVIILL HP LFCATGLOVSYLTWGVLOERVMTRSY-GATATSPGERFTDSOFLVLMNRVLALIVA--GL 10 CE LFFFSGIOVTLVAMGVLQERIITRGYRRSDQLEVEDKFGETQFLIFCNRIVALVLSLMIL HP SCVLCKOPRHGAPMYRYSFASLSNVLSSWCQYEALKFVSFPTQVLAKASKVIPVMLMGKL ***.* .*.* .*..*.******************** CE AKDWTKOPPHVPPLYVHSYTSFSNTISSWCQYEALKYVSFPTQTICKASKVVVTMLMGRL HP VSRRSYEHWEYLTATLISIGVSMFLLSSGPEPRSSPAT--TLSGLILLAGYIAFDSFTSN 15 CE VRGQRYSWFEYGCGCTIAFGASLFLLSSSSKGAGSTITYTSFSGMILMAGYLLFDAFTLN HP WQDALFAYK--MSSVQMMFGVNFFSCLFTVGSLLEQGALLEGTRFMGRHSEFAAHALLLS **.***. * .*. ******** .. . **.**.** . * .*.** 20 CE WOKALFDTKPKVSKYOMMFGVNFFSAILCAVSLIEQGTLWSSIKFGAEHVDFSRDVFLLS HP ICSACGQLFIFYTIGQFGAAVFTIIMTLRQAFAILLSCLLYGHTVTVVGGLGVAVVFAAL ...* **.**. **..**. **..** * CE LSGAIGQIFIYSTIERFGPIVFAVIMTIRQIFIRNTLIRAEDHRGVEMAPPPPPEPFRLK HP LLRVYARGRLKQRGKKAVPVESPVQKV 25

CE FLSMIIAVIHI

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. Z46196) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the

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present invention.

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<HP10671> (SEQ ID NOS: 127, 137, and 147)

Determination of the whole base sequence of the cDNA insert of clone HP10671 obtained from cDNA library of human thymus revealed the structure consisting of a 74-bp 5'-untranslated region, a 921-bp ORF, and a 232-bp 3'-untranslated region. The ORF encodes a protein consisting of 306 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the intermediate region. Figure 47 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA357141) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10673> (SEQ ID NOS: 128, 138, and 148)

Determination of the whole base sequence of the cDNA insert of clone HP10673 obtained from cDNA library of the human thymus revealed the structure consisting of a 203-bp 5'-untranslated region, a 1668-bp ORF, and a 339-bp 3'untranslated region. The ORF encodes a protein consisting of 555 amino acid residues and there existed one putative transmembrane 48 domain. Figure depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product

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of 65 kDa that was somewhat larger than the molecular weight of 61,781 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R96413) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

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<HP10675> (SEQ ID NOS: 129, 139, and 149)

Determination of the whole base sequence of the cDNA insert of clone HP10675 obtained from cDNA library of the human thymus revealed the structure consisting of a 92-bp 5'-untranslated region, a 753-bp ORF, and a 648-bp 3'-untranslated region. The ORF encodes a protein consisting of 250 amino acid residues and there existed at least one putative transmembrane domain. Figure 49 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA356139) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

<HP10683> (SEQ ID NOS: 130, 140, and 150)

30 Determination of the whole base sequence of the cDNA insert of clone HP10683 obtained from cDNA library of the human lymphoma cell line U937 revealed the structure

consisting of a 25-bp 5'-untranslated region, a 525-bp ORF, and a 714-bp 3'-untranslated region. The ORF encodes a protein consisting of 174 amino acid residues and there existed one putative transmembrane domain. Figure 50 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 22 kDa that was somewhat larger than the molecular weight of 19,572 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 24 kDa to which sugar chains are presumably attached. In addition, there exist in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Ile-Thr at position 27).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA482321) among ESTs. However, since they are partial sequences, it can not be judged whether or not they encode the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

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The present invention provides human proteins having hydrophobic domains, DNAs encoding these proteins, and expression vectors for these DNAs as well as eukaryotic cells expressing these DNAs. Since all of the proteins of the present invention are secreted or exist in the cell membrane, they are considered to be proteins controlling the proliferation and/or the differentiation of the cells. Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents

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which control the proliferation act to and/or differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present invention can be utilized as probes for the diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for large-scale expression of these proteins. Cells into which these genes are introduced to express these proteins, can be utilized for detection of the corresponding receptors or ligands, screening of novel small molecule pharmaceuticals and the like.

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The present invention also provides genes corresponding to polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed which to produce the mRNAs from CDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or sequence information from the disclosed identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The

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desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, Trends Pharmacol. Sci. 15(7): Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with qenetic constructs that are stably maintained within the their transformed cells and progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 Bl, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. USA 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153;

5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

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Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75%

sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

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Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the Table 32 below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Table 32

Stringency	Polynucleotide	Hybrid	Hybridization Temperature	Wash
Condition	Hybrid	Length	and Buffer [†]	Temperature
		(bp) [‡]		and Buffer [†]
A	DNA: DNA	≥50	65℃; 1×SSC -or-	65°C; 0.3×SSC
			42°C; 1×SSC,50% formamide	<u> </u>
В	DNA : DNA	<50	T _B *; 1×SSC	T _B *; 1×SSC
C	DNA: RNA	≥50	67°C; 1×SSC -or-	67℃; 0.3×SSC
			45°C; 1×SSC,50% formamide	
D	DNA: RNA	<50	T _D *; 1×SSC	T _D *; 1×SSC
E	RNA: RNA	≥50	70°C; 1×SSC -or-	70°C; 0.3×SSC
			50°C; 1×SSC,50% formamide	
F	RNA: RNA	<50	T _F *; 1×SSC	T _F *; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or-	65°C; 1×SSC
			42°C; 4×SSC,50% formamide	
H	DNA : DNA	<50	T _H *; 4×SSC	T _H *; 4×SSC
Ī	DNA : RNA	≥50	67°C; 4×SSC -or-	67°C; 1×SSC
			45°C; 4×SSC,50% formamide	
J	DNA : RNA	<50	T _J *; 4×SSC	T _J *; 4×SSC
K	RNA: RNA	≥50	70°C; 4×SSC -or-	67°C; 1×SSC
			50°C; 4×SSC,50% formamide	
L	RNA: RNA	<50	T _L *; 2×SSC	T _L *; 2×SSC
М	DNA : DNA	≥50	50°C; 4×SSC -or-	50°C; 2×SSC
			40°C; 6×SSC,50% formamide	
N	DNA : DNA	<50	T _N *; 6×SSC	T _N *; 6×SSC
0	DNA: RNA	≥50	55°C; 4×SSC -or-	55°C; 2×SSC
			42°C; 6×SSC,50% formamide	
P	DNA : RNA	<50	T _P *; 6×SSC	Tp*; 6×SSC
Q	RNA: RNA	≥50	60°C; 4×SSC -or-	60°C; 2×SSC
-			45°C; 6×SSC,50% formamide	
R	RNA: RNA	<50	T _R *; 4×SSC	T _R *; 4×SSC

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‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after

hybridization is complete.

* T_B - T_R : The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m (°C)=2(#of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m (°C)=81.5 + 16.6(log₁₀[Na*]) + 0.41 (%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na*] is the concentration of sodium ions in the hybridization buffer ([Na*] for 1×SSC=0.165M).

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Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of invention to the present which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing

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polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

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CLAIMS

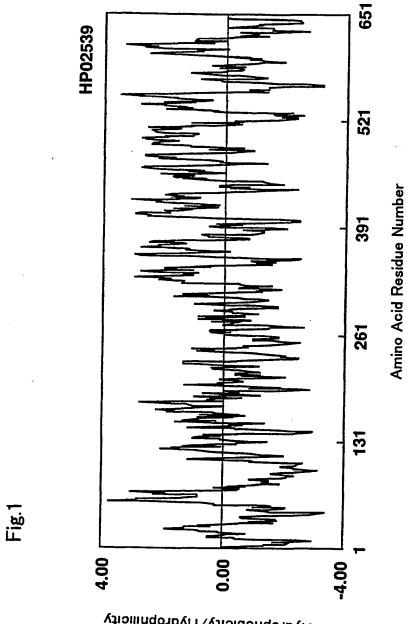
1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.

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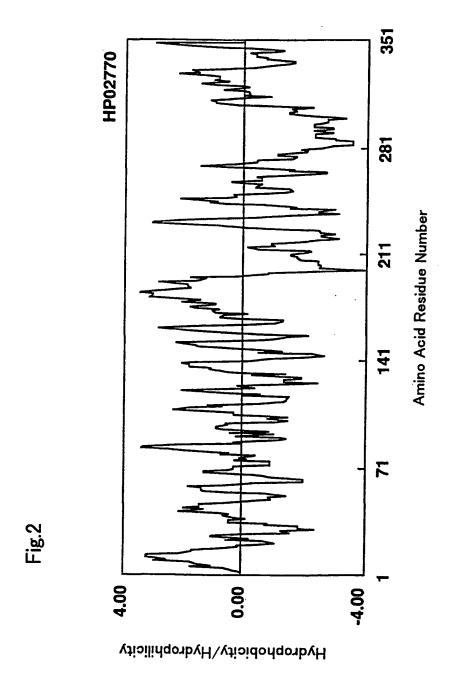
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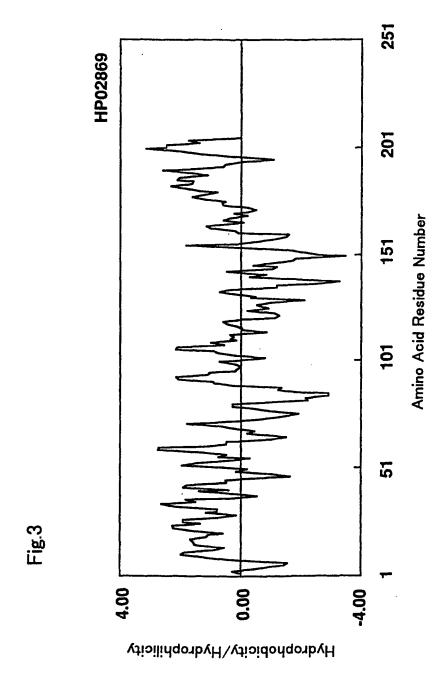
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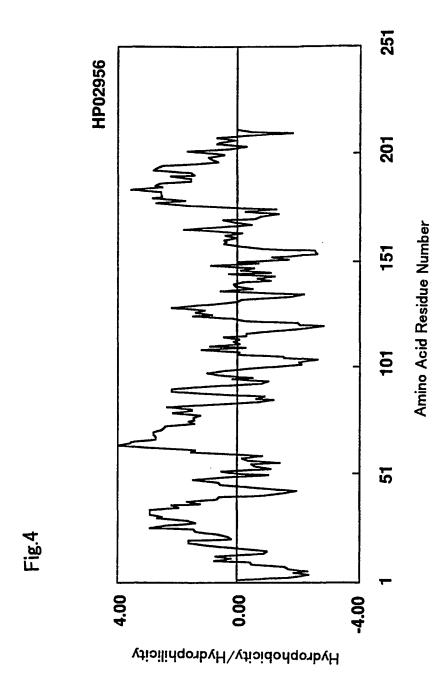
- 2. An isolated DNA encoding the protein according to Claim 1.
- 3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID NOS: 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140.
- 4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID NOS: 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150.
- 5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eukaryotic cells.
 - 6. A transformed eukaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 and of producing the protein according to Claim 1.

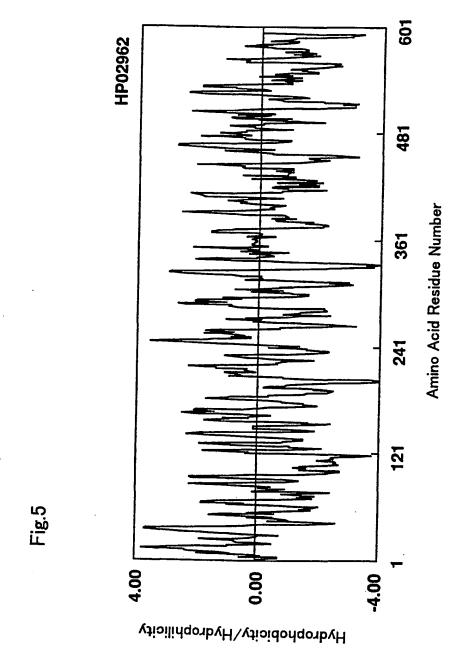


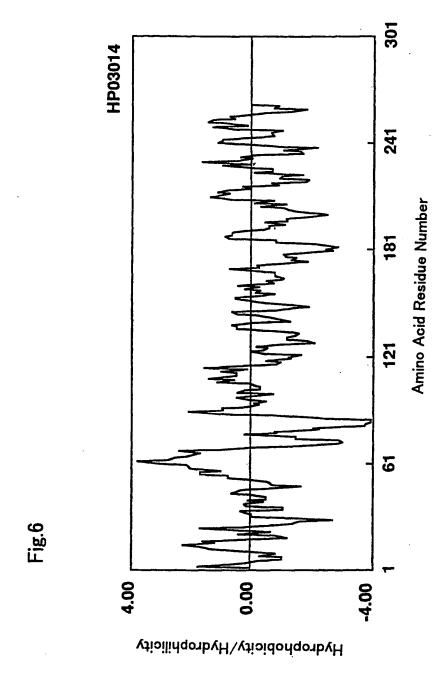
Hydrophobicity/Hydrophilicity

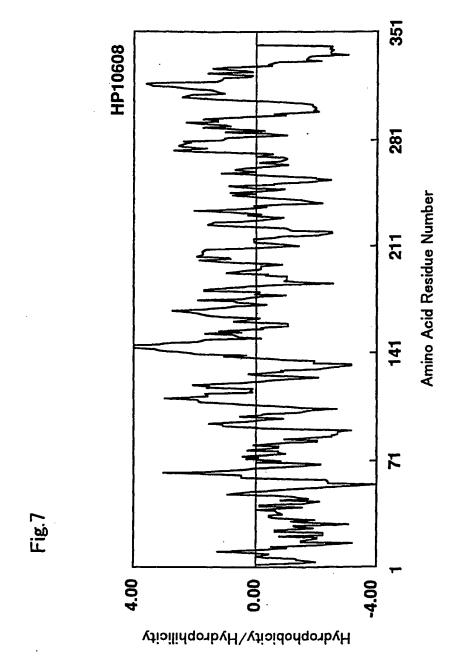


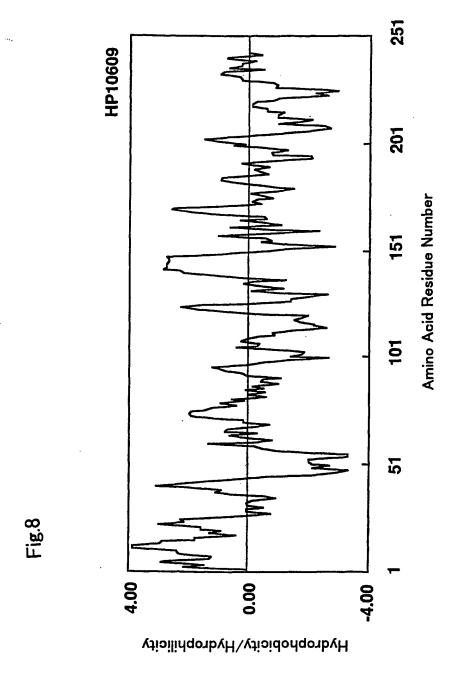


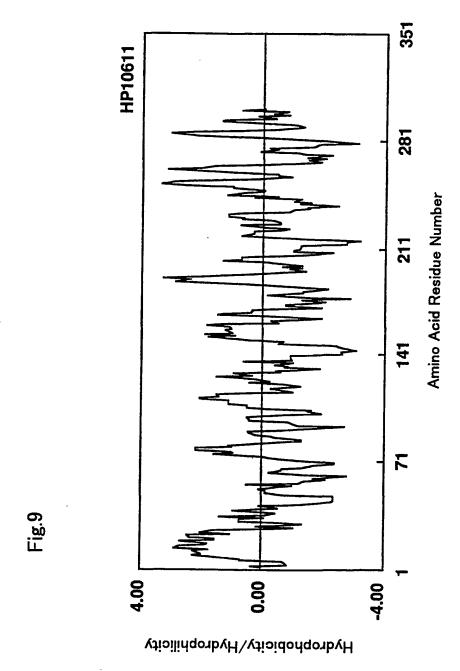


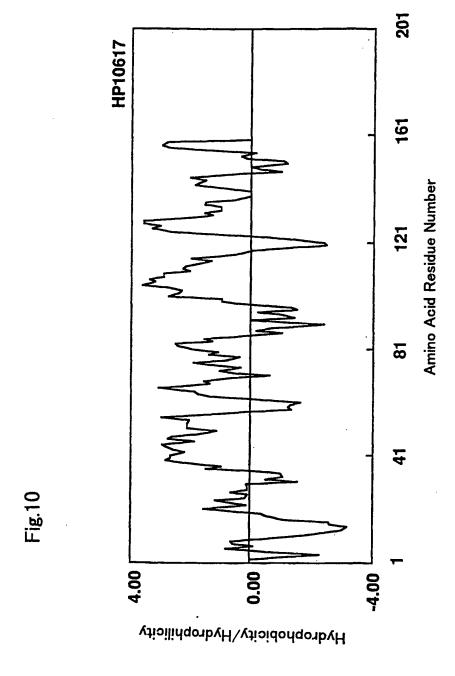


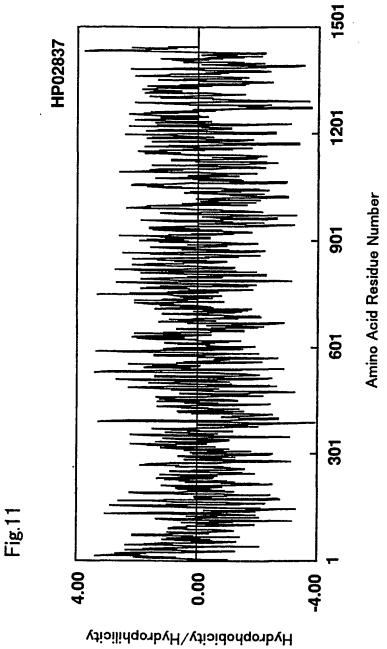


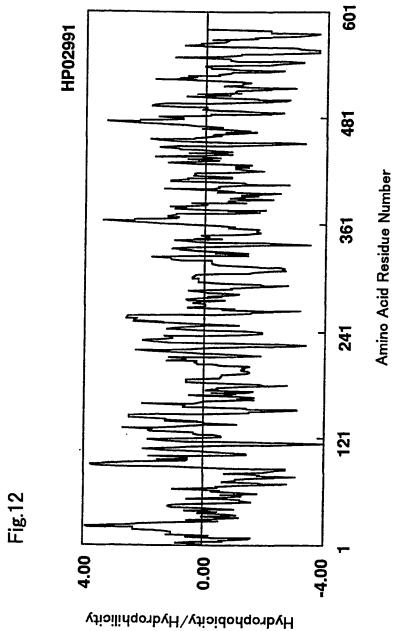


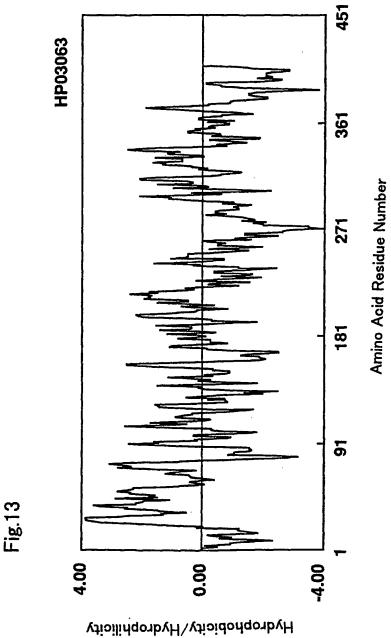


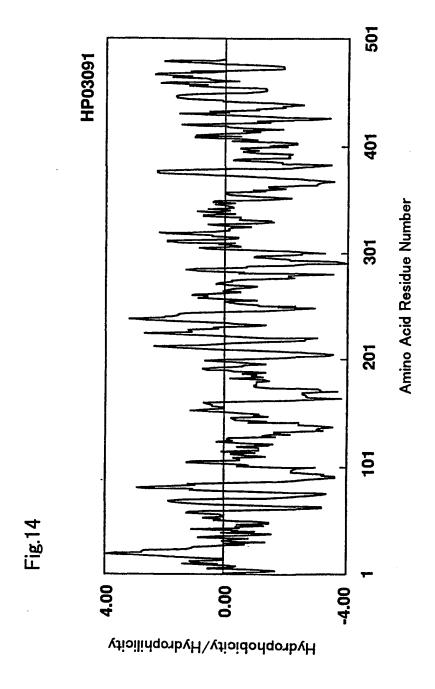


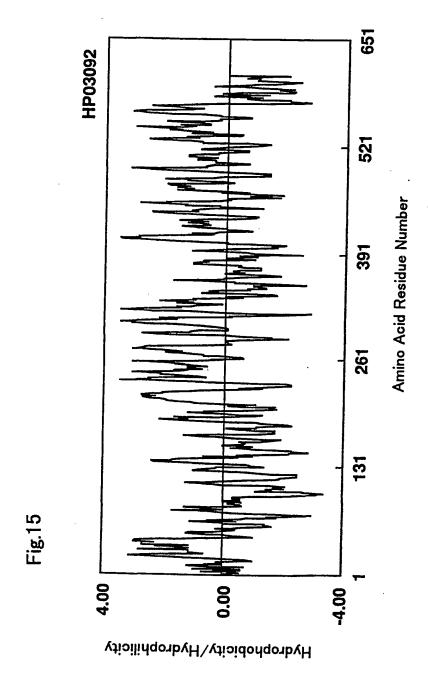


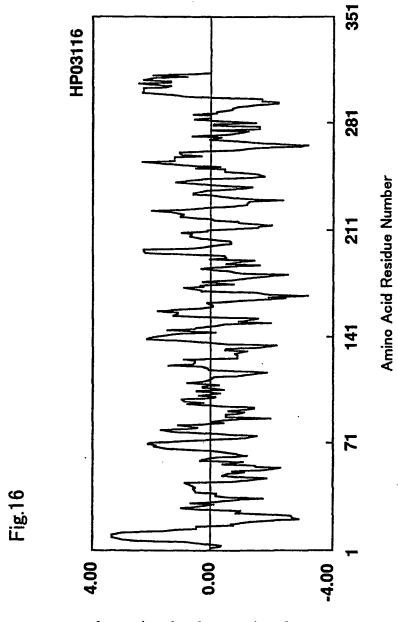




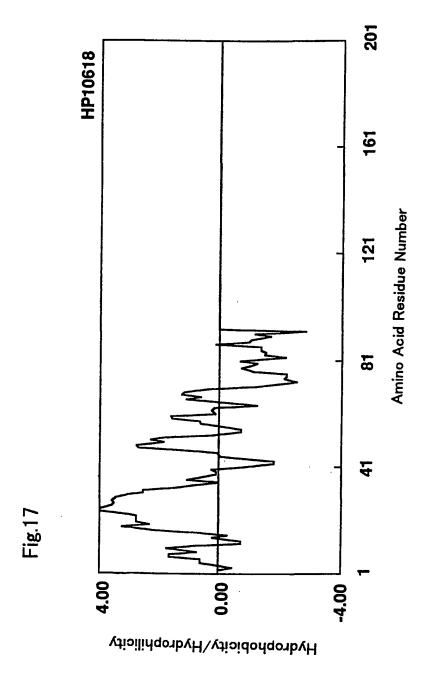


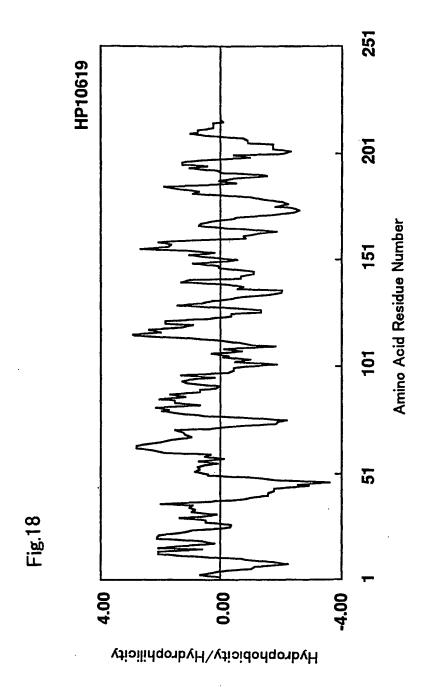


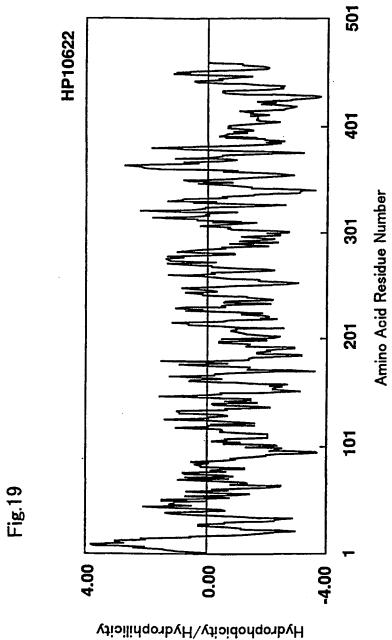


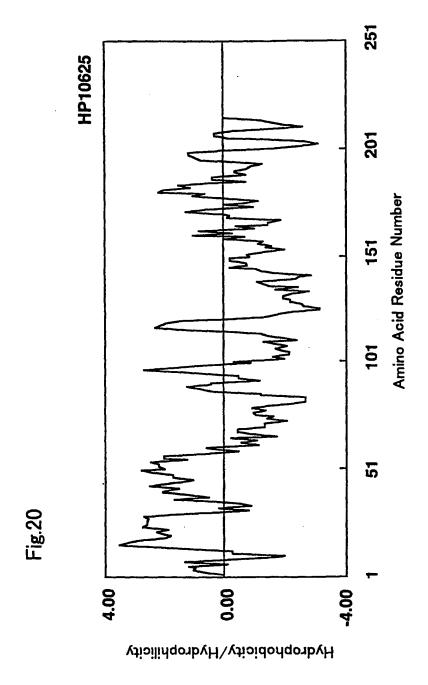


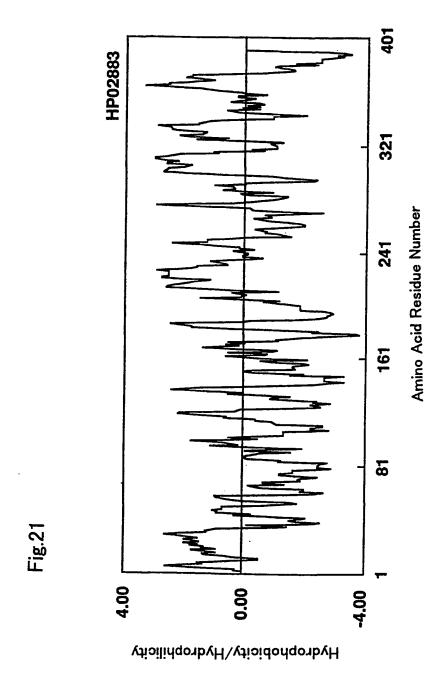
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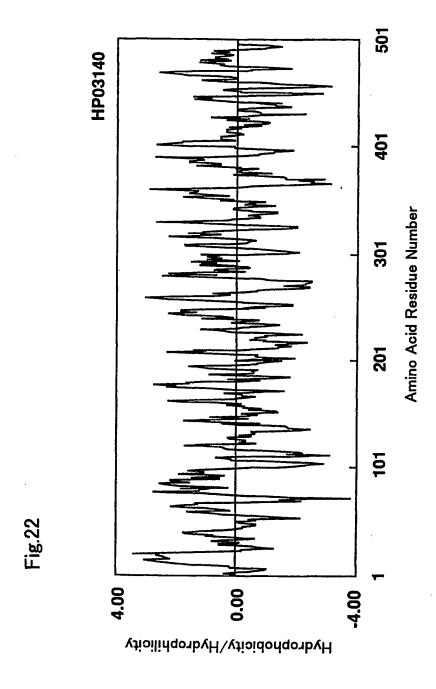


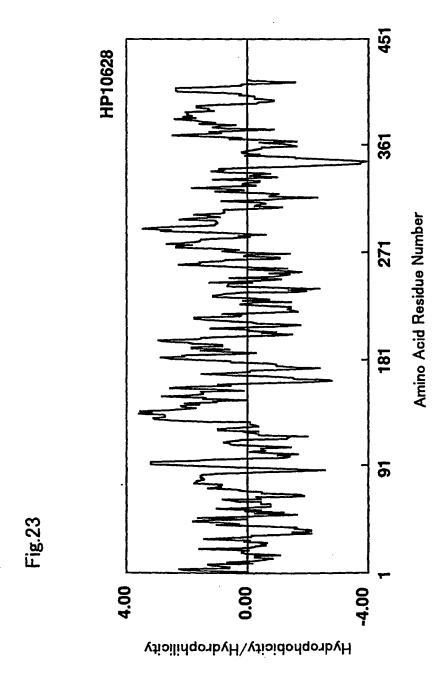


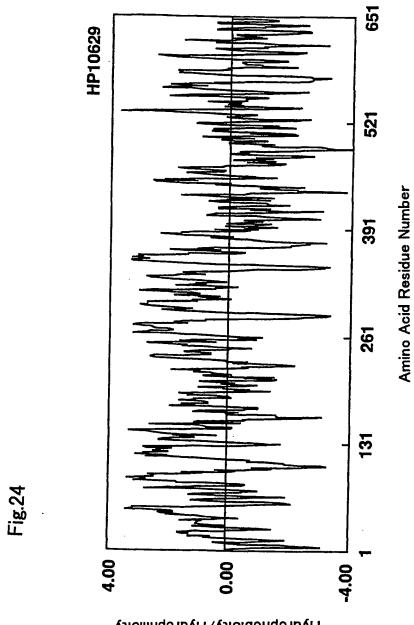




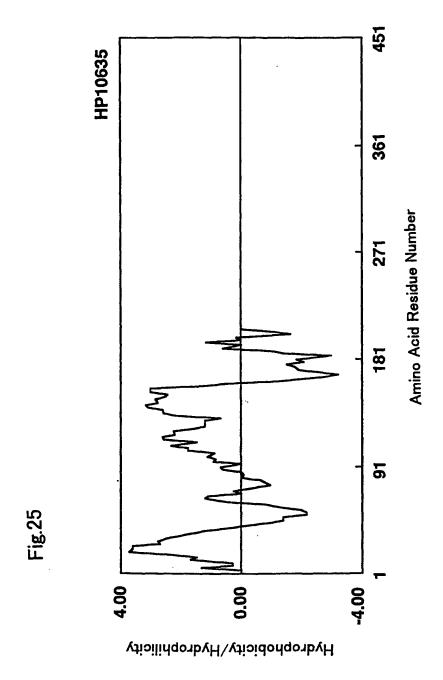


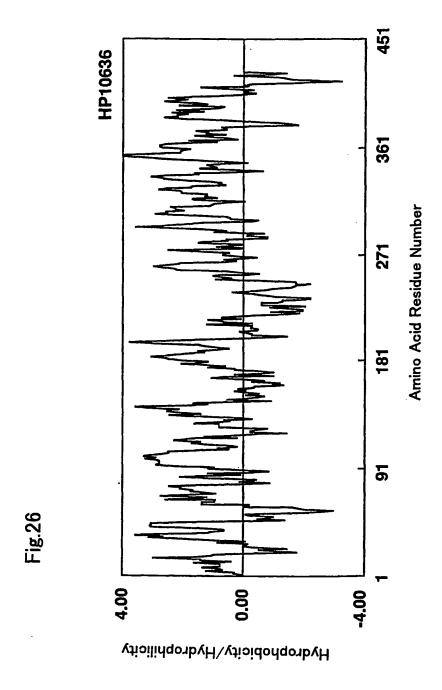


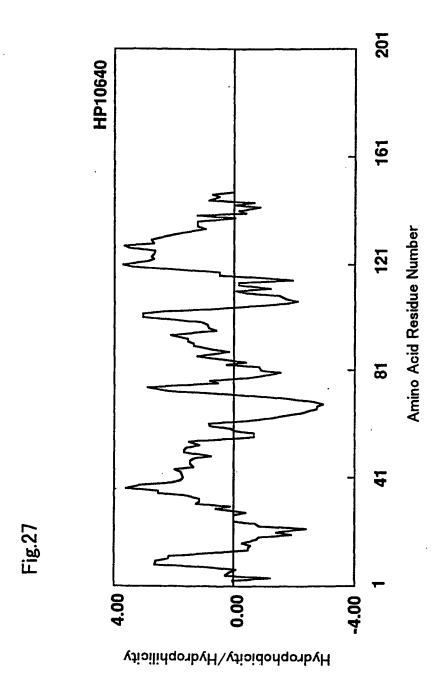


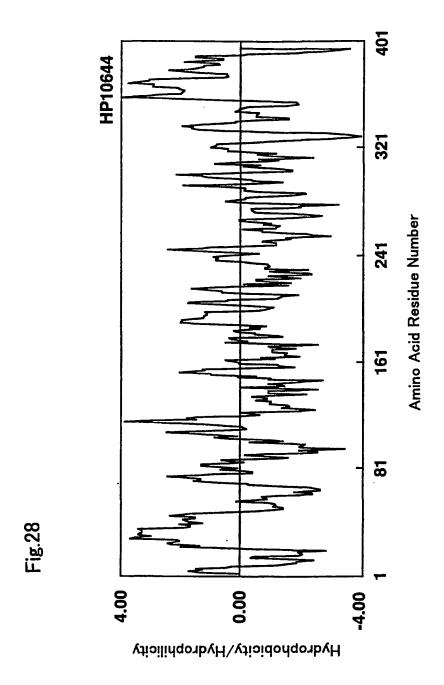


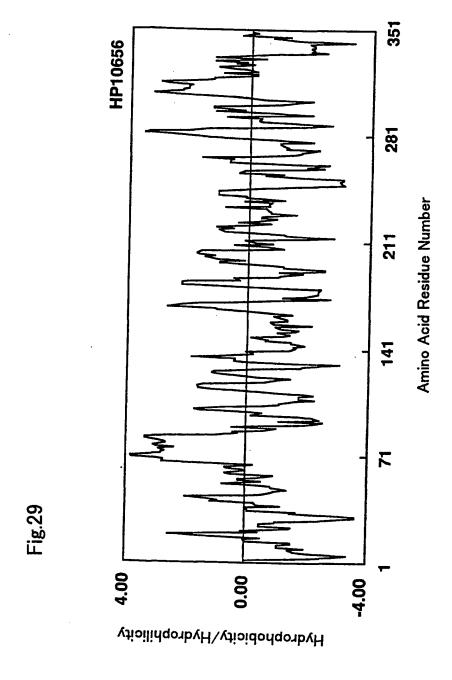
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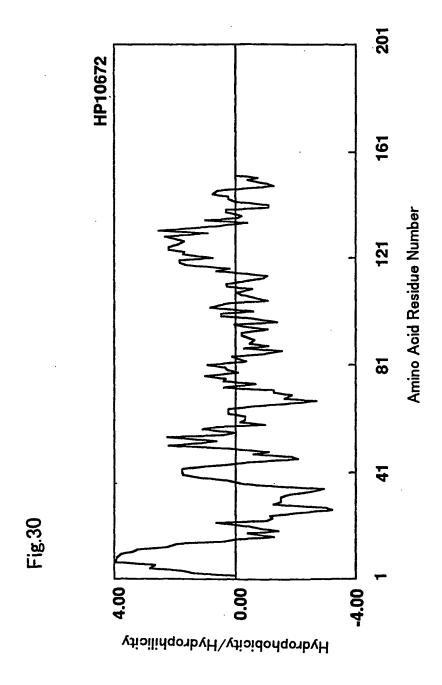


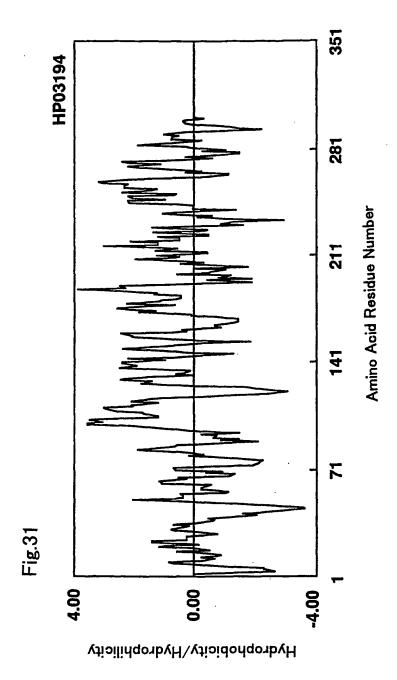


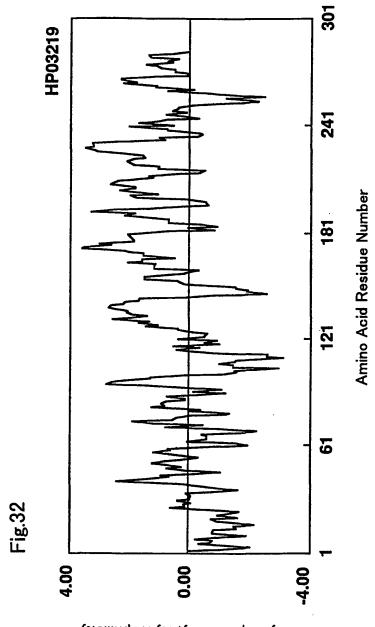




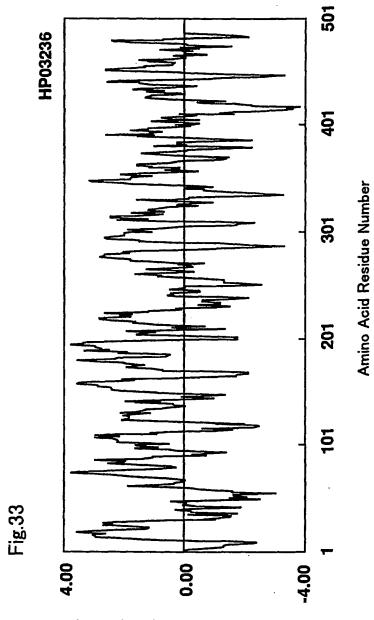




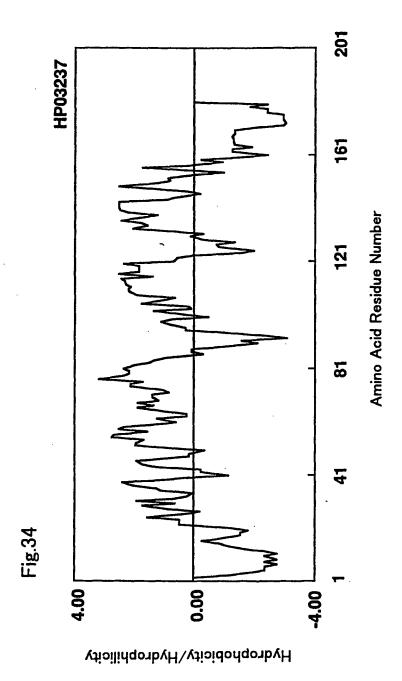


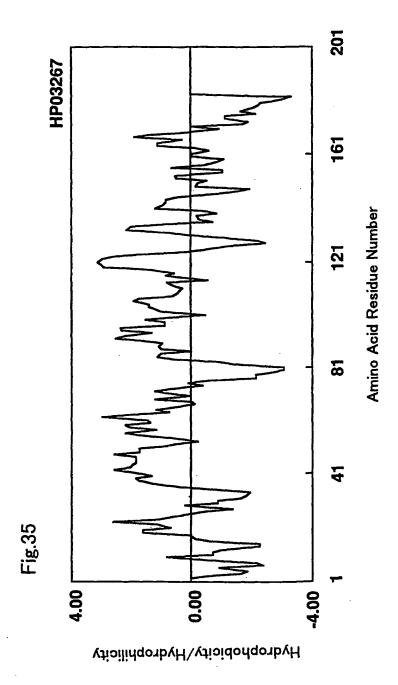


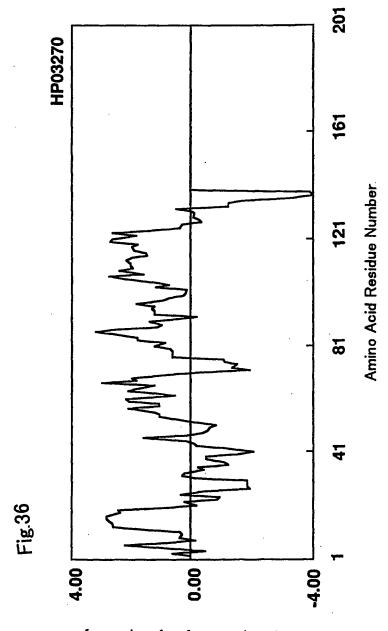
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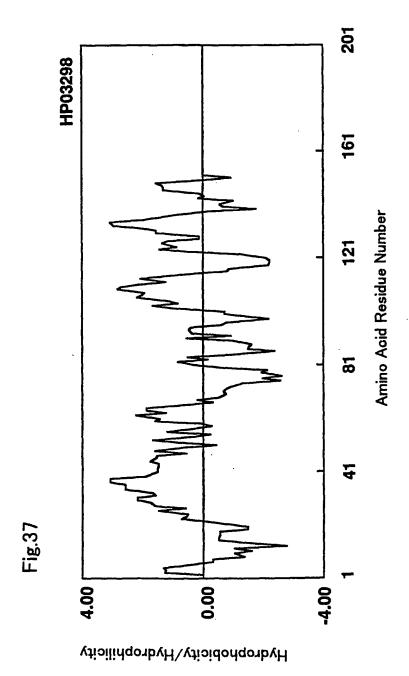
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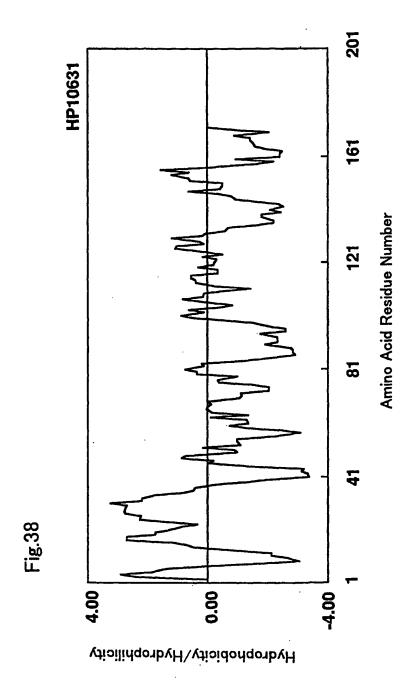


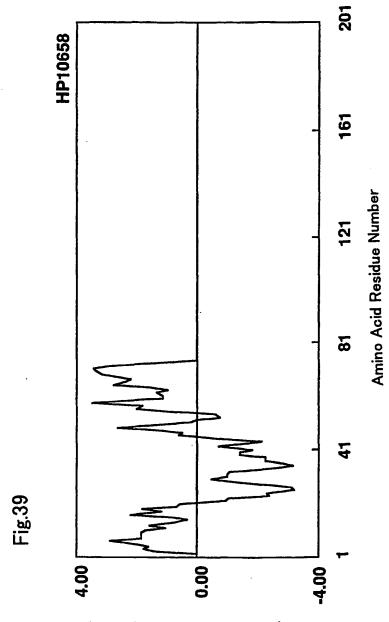




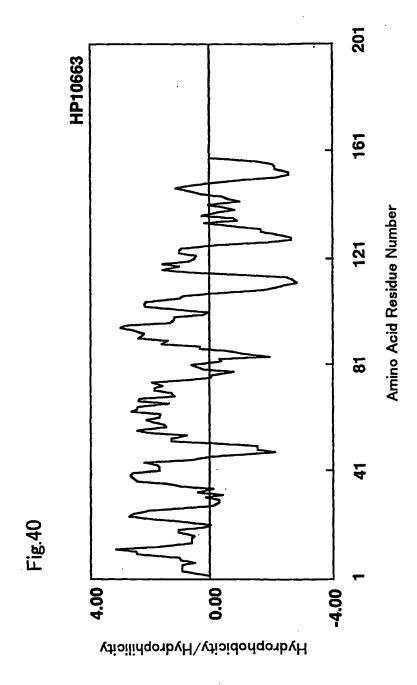
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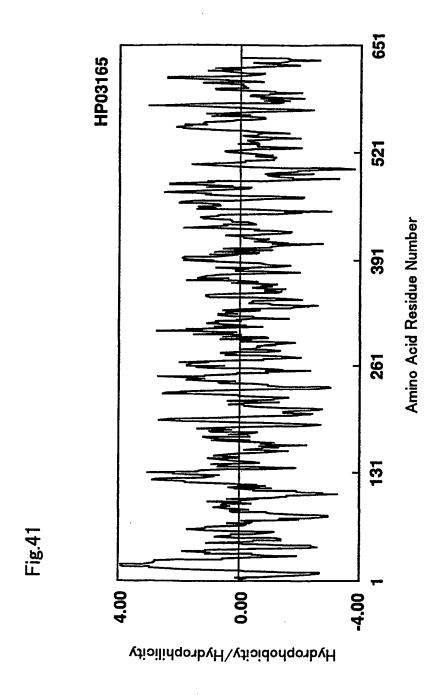


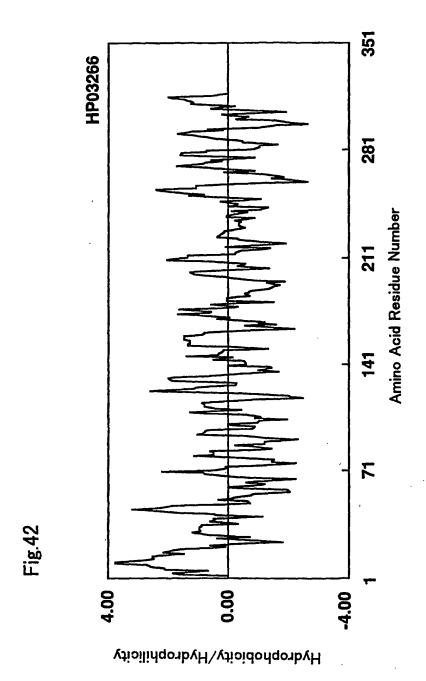


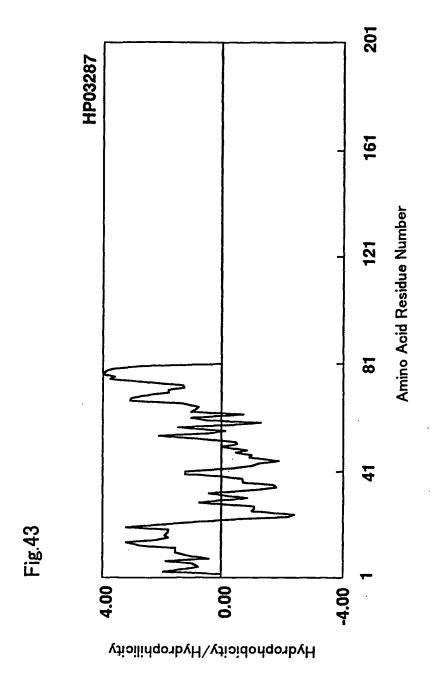


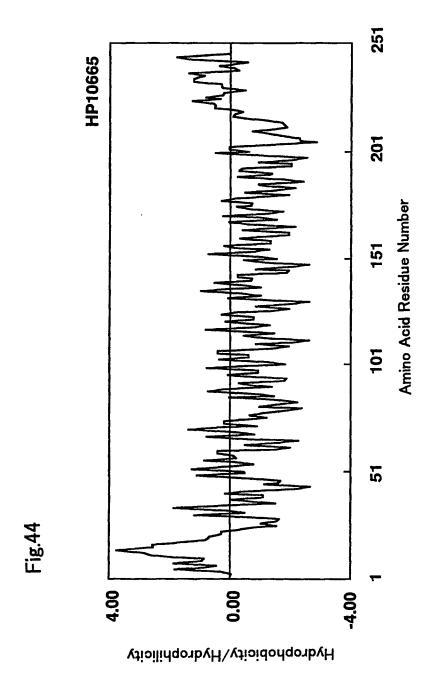
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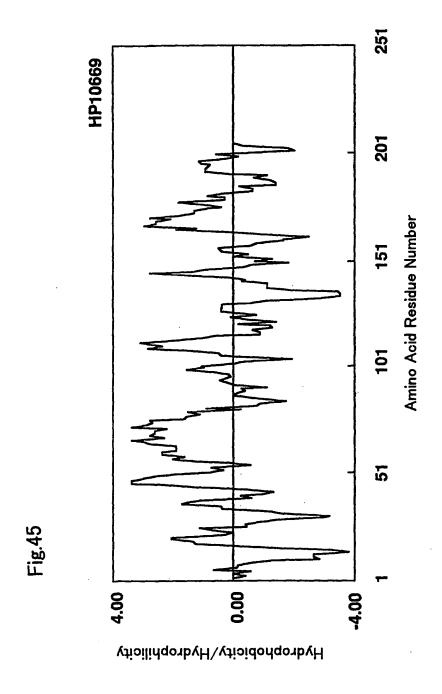


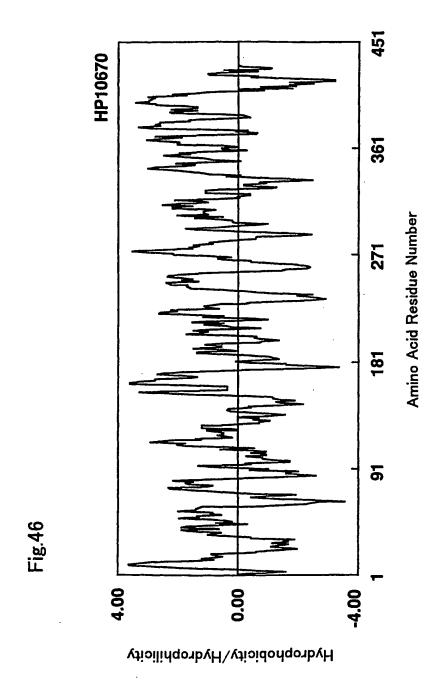


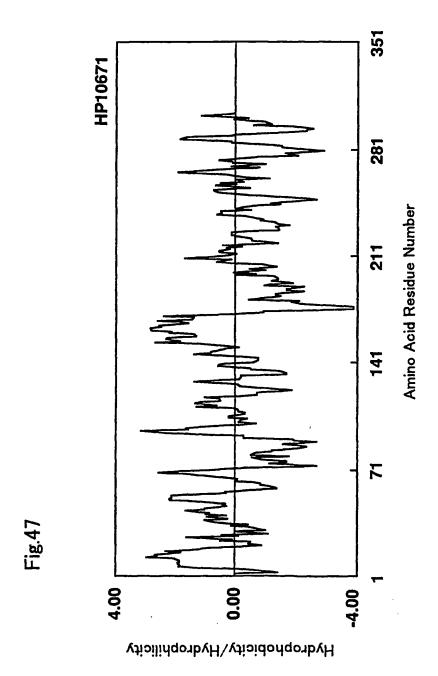


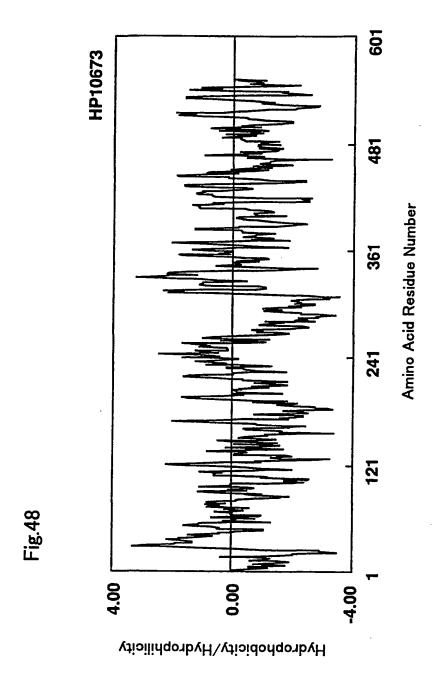


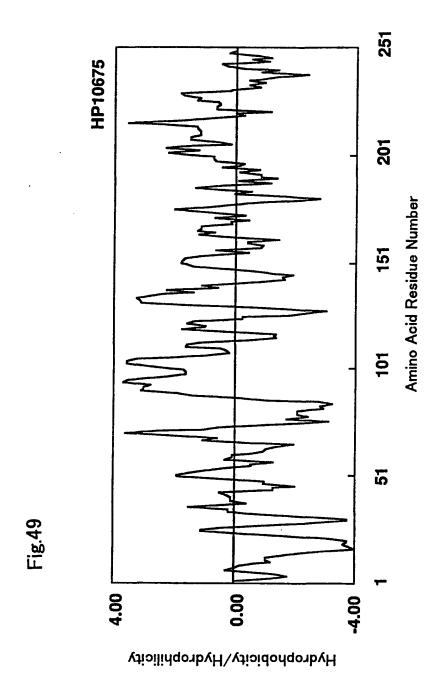


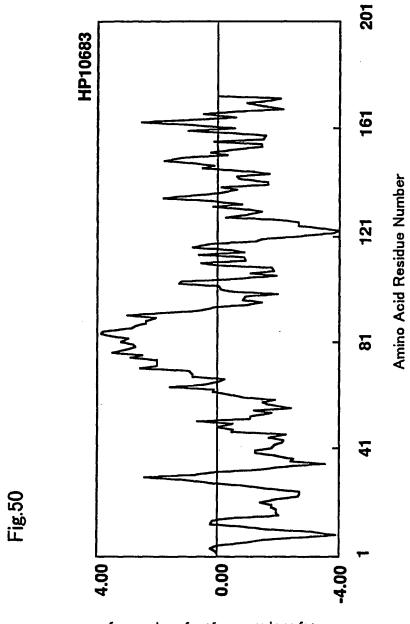












Hydrophobicity/Hydrophilicity

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	·	~··	ם [ת	መኮ~	X	***	N an	1707	700	A	mb	mL	C111	Mot	Len

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Gln	Glu	Trp	Leu	Ala	Ala	Val	Gly	Asp	Asp	Tyr	Ala	Ala	Val	Val	Trp
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Gly	Gln	Gly	Leu	Pro	Val	Val	Ala	Pro	Met	Leu	Asp	Ser	Gln	Thr	Tyr
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Tyr	Ser	Asn	Phe	Trp	Cys	Gly	Ile		Pro	Gln	Gly	Tyr	Tyr	Arg	Arg
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Thr	Ala		Tyr	Phe	Pro	Thr	_	Asn	Arg	Gln	Arg		Gly	Сув	Phe
	· •	195		-		_	200		_		_	205		_ •	
Arg		Pro	Met	Val	His		Thr	Phe	Leu	Ala		Leu	Arg	Ala	GIU
— 3 —	210	•	-1.	•		215	_			 1 _	220	3		m\	
_	ALA	Asp	GIN	ren		Pne	туг	PLO	Pro		PIO	ASII	Tyr	THE	240
225	Db.o		3 ~~	T1.	230	***	The s	21-	M	235	~	Cln	አገል	ת ה	
PIO	Pue	мар	Азр	245	116	val	Pne	MIG	250	MIG	cys	GIII	Ala	255	GLY
Val	Sar	Ta7	ui e		Cve	Aan	Gl 11	vi a		(Tear)	Glv	ጥረታት	Met		
vaı	Der	val	260	Val	Cys	ASII	GIU	265	AL 9	TYL	GIŢ	17.	270	re:	Val
Pro	Val	Twe		Hia	Gln	Glv	T.e.11	_	Agn	Glu	Ara	Val	Asn	Phe	Tle
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Leu	Val	Val	Ala	Gly	Tyr	Ser	Tyr	Trp	Thr	Leu	Ala	Tyr	Ala	Leu	Arg
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Tyr	Arg	Leu	Lys	Leu	Glu	Glu	Leu	Thr	Lys	Leu	Gln	Asn	Asn	Суз	Thr
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Thr	Phe	Leu	Leu	Pro	Phe	Leu	Phe	Phe	Gly	His	Phe	Trp	Gln	Leu	Phe
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20
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Cys Leu Pro Pro Leu Arg Ala Ala Ala Glu Gln Leu Arg Gln Lys Asp

35
40
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Pro Ala Gln Pro Pro Glu Pro Glu Ala Leu Pro Thr Ile Tyr Val Val

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Val		Cys	Ser	Ala	Glu		Lys	Phe	Phe	Leu	- -	Ser	Met	Tyr	Ala	
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	Val	Суз	Thr	Val		Glu	Gln	Ala	Leu		Pro	Суз	Arg	Ser		
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_	-		gcg	-	_	_	-	-	-							806
сув	GIU	Arg	Ala	_	GIN	СТА	Cys	GIU		Leu	Met	ASN	тув		GīÅ	
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			cca	-	-		_	_		-						034
rne	GIII	Trp	Pro	Asp	THE	red	гĂа		GIU	гля	PILE	PLO	220	UTS	GTÅ	
400	~~~	~~~	210	+ ~~	~+~			215	200	taa	gao.	-94		800	664	902
_			ctg Leu	_			-		-		_	_				JU2
AIG	GIÀ	225	Leu	cys	vaı	GIY	230	Asn	THE	Set	ASP	235	GIY	1111	710	
200			ctg	-++		~~~		+ ~~	500	944	225		~~	727	aaa	950
-		_	Leu							_			_			,,,,
1111	240	SeT	reu	пеп	PIO	245	PHE	тъ	TILL	Per	250	PIO	GIII	птэ	GIY	
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	-		cac	-				-								,,,,
955 255	атА	ату	His	_	260 GIÀ	GTÅ	FIIO	5TO	отА	265	νια	GTĀ	vra	ner	270	
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Asp	гàз		Ala	GIU	qeA	GIĀ		Arg	Thr	vaı	Ala		GIÀ	THE	гла	
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			-					atg	_							1430
гÃа		СТĀ	сув	THE	TTE		Pne	Met	Met	Leu		Pue	Pne	Ser	Mec	
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415	Ser	SET	TTE	πÞ	420	Val	TTE	Leu	Ser	425	1111	тъ	FILE	пеп	430	
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-		_	_					Ala		-	-			_		1320
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+++	CAC	cta	acc		taa	act	ata	ccg		ato	apa'	800	ata		atc	1574
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E 110											-y 0					

			450)				455	i				460)		
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26/233

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Lys		Сув	Gly	Ala	Gly		Gly	Ala	Gly	Pro	_	Leu	Ala	Trp	Ala	
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Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala 15 20 25 gtt gte tte ett gga gte ggg etg tgg gea tgg age gaa aag ggt Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly 35 40 45 etg tee gae ete ace aaa gtg ace egg atg eat gga atc gae eet Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro	gga 158 Gly 30 gtg 206 Val gtg 254 val gcc 302
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys  1 5 10  tac aag tac ctc ctt ttc agc tac aac atc atc ttc tgg ttg gct Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala 15 20 25  gtt gtc ttc ctt gga gtc ggg ctg tgg gca tgg agc gaa aag ggt Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly  35 40 45  ctg tcc gac ctc acc aaa gtg acc cgg atg cat gga atc gac cct Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro  50 55 60  gtg ctg gtc ctg atg gtg gtg atg ttc acc ctg ggg ttc Val Leu Val Leu Met Val Gly Val Val Met Phe Thr Leu Gly Phe	gga 158 Gly 30 gtg 206 Val gtg 254 Val gcc 302 Ala
Met His Tyr Tyr Arg Tyr Ser Asn Ala Lys Val Ser Cys  1 5 10  tac aag tac etc ett tte age tac aac atc atc tte tgg ttg get Tyr Lys Tyr Leu Leu Phe Ser Tyr Asn Ile Ile Phe Trp Leu Ala 15 20 25  gtt gtc ttc ett gga gtc ggg etg tgg gca tgg age gaa aag ggt Val Val Phe Leu Gly Val Gly Leu Trp Ala Trp Ser Glu Lys Gly 35 40 45  etg tec gac etc acc aaa gtg acc egg atg eat gga atc gac ect Leu Ser Asp Leu Thr Lys Val Thr Arg Met His Gly Ile Asp Pro 50 55 60  gtg etg gtc etg atg gtg ggc gtg gtg atg ttc acc etg ggg ttc Val Leu Val Leu Met Val Gly Val Val Met Phe Thr Leu Gly Phe 65 70 75	gga 158 Gly 30 gtg 206 Val gtg 254 Val gcc 302 Ala aac 350

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Met Val Ala Ser Ala Lys Met Gly Arg  1 5  gea ggg acc atg geg gtg gea gea gag ett ega gag etg tge eea gga Ala Gly Thr Met Ala Val Ala Ala Glu Leu Arg Glu Leu Cys Pro Gly 10 15 20 25  gtg aac aac eag eec tac etc tgt gag agt ggt eac tge tge ggg gag Val Asn Asn Gln Pro Tyr Leu Cys Glu Ser Gly His Cys Cys Gly Glu act gge tge tge acc tac tac tat gag etc tgg tgg tte tgg etg etc Thr Gly Cys Cys Thr Tyr Tyr Tyr Glu Leu Trp Trp Phe Trp Leu Leu 45 50 55  tgg act gte etc eac ega eac ega	101 149 197
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Val	Ala	Pro	Gly	Arg	Pro	Leu	Thr	Ala	Ser	Ser	Glu	Gln	Thr	Суз	Суз	
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Gln	Ile	Phe	Pro	Met	Gly	Leu	Ser	Ser	Ser	Glu	Gly	Asp	Ile	Pro		
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+	atao	++++	n an	edaa	taas	tac	ratts	ott	aaaa			" ORTRI	ccct	'A		870

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Gln Glu Thr His Arg Leu Tyr Arg Leu Lys Leu Glu Glu Leu Thr Lys	
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His	Phe	Trp	Gln	Leu	Phe	Asn	Ala	Leu	Thr	Leu	Phe	Asn	Leu	Ala	Gln	
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Leu Leu Gln Leu Leu Val Leu Leu Leu Thr Leu Pro Leu His Leu Met	
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Lys Arg Glu Leu Phe Ser Gln Ile Lys Gly Leu Thr Gly Ala Ser Gly	
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Phe	Glu	Lys	Phe	Leu	Thr	Lys	Ser	Met	Ala	Glu	Asn	Arg	His	Leu	Gln	
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Gln	Ser	Pro	Arg	Lys	Val	Leu	Gln	Glu	Val	Arg	Arg	Val	Leu	Arg	Pro	
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aac gtg Asn Val gcg ctg Ala Leu gca gca Ala Ala 40 caa gcg Gln Ala	ttt Phe gta Val 25 gcc Ala gaa Glu	ctc Leu 10 cag Gln gag Glu ctc Leu	gec Ala etc Leu cag Gln cga Arg	tac Tyr ggc Gly cta Leu cgg Arg 60 act	ttc Phe cag Gln cgg Arg 45 cca Pro	ctg Leu cca Pro 30 cag Gln ccc Pro	gtg Val 15 tgt Cys aag Lys cct Pro	tcg Ser gac Asp gat Asp	Medicate Ilea tgc Cys ctg Leu cct Pro 65 acc	t Lys gec Ala ett Leu agg 50 gec Ala cec	ggc Gly cct Pro 35 att Ile cag Gln acc	ctc Leu 20 ccc Pro tcc Ser ccc Pro	teu etg Leu eag Gln ect Pro	tac Tyr cgg Arg ctg Leu gaa Glu 70 agg	103 151 199 247

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Pro	Leu	Trp	Val	Gln	Tyr	Pro	Gln	Aap	Val	Thr	Thr	Phe	Asn	Ile	Asp		
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Tyr	Leu	Pro	Val	Thr	Leu	Ser	Ser	Ile	Pro	Val	Phe	Gln	Arg	Gly	Gly		
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Thr	Ile	Val	Pro	Arg	Trp	Met	Arg	Val	Arg	Arg	Ser	Ser	Glu	Сув	Met		
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aag	gat	gac	ccc	atc	act	ctc	ttt	gtt	gca	ctt	agc	cct	cag	ggt	aca	63	1
Lys	Asp	qaA	Pro	Ile	Thr	Leu	Phe	Val	Ala	Leu	Ser	Pro	Gln	Gly	Thr		
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gct	caa	gga	gag	ctc	ttt	ctg	gat	gat	ggg	cac	acg	ttc	aac	tat	cag	67	9
Ala	Gln	Gly	Glu	Leu	Phe	Leu	Asp	Asp	Gly	His	Thr	Phe	Asn	Tyr	Gln		
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act	cgc	caa	gag	ttc	ctg	ctg	cgt	cga	ttc	tca	ttc	tct	ggc	aac	acc	72	7
Thr	Arg	Gln	Glu	Phe	Leu	Leu	Arg	Arg	Phe	Ser	Phe	Ser	Gly	Asn	Thr		
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Leu	Val	Ser	Ser	Ser	Ala	Asp	Pro	Glu	Gly	His	Phe	Glu	Thr	Pro	Ile		
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Trp	Ile	Glu	Arg	Val	Val	Ile	Ile	Gly	Ala	Gly	Lys	Pro	Ala	Ala	Val		
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7e7	T.DII	G) n	ጥኮሎ	Tara	G) v	Sor	Dro	Glu	Ser	Ara	Tan	502	Dha	Gln	uia		

265 270 275	
gae cet gag ace tet gtg ttg gte etg ege aag eet gge ate aat gtg	919
Asp Pro Glu Thr Ser Val Leu Val Leu Arg Lys Pro Gly Ile Asn Val	
280 285 290	
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Ala Ser Asp Trp Ser Ile His Leu Arg	
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			M	et A	sp Ly	ys L	eu Ly	ys L	ys V	al L	eu S	er G	ly G	ln A	sp Th	r
				1				5					10			
gag	gac	cgg	agc	ggc	ctg	tcc	gag	gtt	gtt	gag	gca	tct	tca	tta	agc	159
Glu	Asp	Arg	Ser	Gly	Leu	Ser	Glu	Val	Val	Glu	Ala	Ser	Ser	Leu	Ser	
	15					20					25					
tgg	agt	acc	agg	ata	aaa	ggc	ttc	att	gcg	tgt	ttt	gct	ata	gga	att	207
Trp	Ser	Thr	Arg	Ile	Lys	Gly	Phe	Iľe	Ala	Сув	Phe	Ala	Ile	Gly	Ile	
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Leu	Cys	Ser	Leu	Leu	Gly	Thr	Val	Leu	Leu	Trp	Val	Pro	Arg	Lys	Gly	
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Leu	His	Leu	Phe	Ala	Val	Phe	Tyr	Thr	Phe	Gly	Asn	Ile	Ala	Ser	Ile	
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Gly	Ser	Thr	Ile	Phe	Leu	Met	Gly	Pro	Val	Lys	Gln	Leu	Lys	Arg	Met	
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Phe	Glu	Pro	Thr	Arg	Leu	Ile	Ala	Thr	Ile	Met	Val	Leu	Leu	Суз	Phe	
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Ala	Leu	Thr	Leu	Суз	Ser	Ala	Phe	Trp	Trp	His	Asn	Lys	Gly	Leu	Ala	
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Leu	Ile	Phe	Сув	Ile	Leu	Gln	Ser	Leu	Ala	Leu	Thr	Trp	Tyr	Ser	Leu	
				130					135					140		
tcc	ttc	ata	cca	ttt	gca	agg	gat	gct	gtg	aag	aag	tgt	ttt	gee	gtg	543
Ser	Phe	Ile	Pro	Phe	Ala	Arg	Asp	Ala	Val	Lys	Lys	Сув	Phe	Ala	Val	
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Суз	Leu	Ala														
		160														
gctg	iatac	jac e	gttt	tgte	a ct	atct	tega	a aac	etet	gtc	ttac	agac	at c	jtgcc	tttta	660
tett	geag	jca a	atgto	jttgo	t to	rtgat	tege	a ace	ttt	gagg	gtte	cttt	tg g	gaago	aacaa	720
taca	ittet	.cg e	acct	gaat	g to	agta	gcac	ago	gatga	ıgaa	gtgg	gtto	tg t	atct	tgtgg	780

agtggaatet teeteatgta cetgttteet etetggatgt tgteceaetg aatteceatg

48/233

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aaa	ggca	gcc	ccat	caga	ga t	cacg	ggag	c aa	cagt	aagg	gac	agag	ttt	tggg	gtcca
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Thr	Ala	Ala	Leu	Ala	Val	Ala	Pro	Gly	Pro	Arg	Phe	Leu	Val	Thr	Ala
			20					25					30		
Pro	Gly	Ile	Ile	Arg	Pro	Gly	Gly	Asn	Val	Thr	Ile	Gly	Val	Glu	Leu
		35					40					45			
Leu	Glu	His	Суз	Pro	Ser	Gln	Val	Thr	Val	Lys	Ala	Glu	Leu	Leu	Lys
	50					55					60				
Thr	Ala	Ser	Asn	Leu	Thr	Val	Ser	Val	Leu	Glu	Ala	Glu	Gly	Val	Phe
65					70					75					80
Glu	Lys	Gly	Ser	Phe	Lya	Thr	Leu	Thr	Leu	Pro	Ser	Leu	Pro	Leu	Asn
				85					90					95	
Ser	Ala	Asp	Glu	Ile	Tyr	Glu	Leu	Arg	Val	Thr	Gly	Arg	Thr	Gln	qaA
			100					105					110		
Glu	Ile	Leu	Phe	Ser	Asn	Ser	Thr	Arg	Leu	Ser	Phe	Glu	Thr	Lys	Arg
		115					120					125			
Ile	Ser	Val	Phe	Ile	Gln	Thr	Asp	Lys	Ala	Leu	Tyr	Lys	Pro	Lys	Gln
	130					135					140				
Glu	Val	Lys	Phe	Arg	Ile	Val	Thr	Leu	Phe	Ser	Asp	Phe	Lys	Pro	Tyr
145					150					155					160
Lys	Thr	Ser	Leu	Asn	Ile	Leu	Ile	Lys	Asp	Pro	Lys	Ser	Asn	Leu	Ile
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Gln	Gln	Trp	Leu	Ser	Gln	Gln	Ser	qeA	Leu	Gly	Val	Ile	Ser	Lys	Thr

WO 00/29448 PCT/JP99/06412

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Gln	Val	Asn	Asp	Gln	Thr	Tyr	Tyr	Gln	Ser	Phe	Gln	Val	Ser	Glu	Туз
	210					215					220				
Val	Leu	Pro	Lys	Phe	Glu	Val	Thr	Leu	Gln	Thr	Pro	Leu	Tyr	Cys	Ser
225					230					235					240
Met	Asn	Ser	Lys	His	Leu	Asn	Gly	Thr	Ile	Thr	Ala	Lys	Tyr	Thr	Туг
				245					250					255	
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			260					265			٠		270		
Phe	Trp	Gly	Lys	Lys	Lys	Asn	Ile	Thr	Lys	Thr	Phe	Lys	Ile	Asn	Gly
		275					280					285			
Ser	Ala	Asn	Phe	Ser	Phe	Asn	Asp	Glu	Glu	Met	Lys	Asn	Val	Met	Asp
	290					295					300				
Ser	Ser	Asn	Gly	Leu	Ser	Glu	Tyr	Leu	Asp	Leu	Ser	Phe	Pro	Gly	
305					310					315					320
Val	Glu	Ile	Leu	Thr	Thr	Val	Thr	Glu		Val	Thr	Gly	Ile		Arg
				325					330					335	
Asn	Val	Ser		Asn	Val	Phe	Phe	_	Gln	His	Asp	Tyr		Ile	Glu
			340					345					350		
Phe	Phe		Tyr	Thr	Thr	Val		Lys	Pro	Ser	Leu		Phe	Thr	Ala
	1	355					360		_			365		- 1	~ 3
TOF		ràa	Val	Thr	Arg		Ąsp	GIĀ	Asn	Gln		Thr	ren	GIU	GIU
3	370	•		**- 1	**7	375	671	**-7	m\	a 1	380			m\	01. .
_	Arg	ASII	ASN	vai		TTe	THE	var	Thr	Gln	Arg	ASII	TYL	THE	
385	(T)	Ca-	<i>~</i> 1••	Cor	390	Cor	C1**	3 an	C1 5	395 Lys	Wa+	~1··	31 0	17-1	400
ıyı	ırp	SET	GTĀ	405	ASII	Ser	GIÀ	ASII	410	тйя	Mec	GIU	MIG	415	GIII
Taro	Tla	λan	The same		tre l	Dro	Cln.	Sor		Thr	Dho	T 170	Tla		Dha
-15	110	VDII.	420	TIM	AGT	FIO	GIII	425	GIY	1111	FIIG	пуз	430	GIU	F 110
Pro	Tle	T.e.u) an	Sor	Sor	Glu		Gln	Leu	Tara	λla		Dha	T.e.it
		435	Jiu	ىيىد	J-134.		440	4004	711	_cu	-Jyo	445	-1-	- 410	
Glv	Ser		Ser	Ser	Met	Ala		His	Ser	Leu	Dhe		Ser	Pro	Ser
1	450	-10	<u>.</u>			A55				_cu	460 1110	-1-			

Lys	Thr	Tyr	Ile	Gln	Leu	Lys	Thr	Arg	Asp	Glu	Asn	Ile	Lys	Val	Gly
465					470					475					480
Ser	Pro	Phe	Glu	Leu	Val	Val	Ser	Gly	Asn	Lys	Arg	Leu	Lys	Glu	Leu
	•			485					490					495	
Ser	Tyr	Met	Val	Val	Ser	Arg	Gly	Gln	Leu	Val	Ala	Val	Gly	ГЛа	Gln
			500					505					510		
Asn	Ser	Thr	Met	Phe	Ser	Leu	Thr	Pro	Glu	Asn	Ser	Trp	Thr	Pro	Lys
		515					520					525			
Ala	_	Val	Ile	Val	Tyr	Tyr	Ile	Glu	Asp	Asp	Gly	Glu	Ile	Ile	Ser
	530					535					540				
_	Val	Leu	Lys	Ile		Val	Gln	Leu	Val		Lys	Asn	Lys	Ile	_
545				_	550		_			555	_		-	_	560
Leu	Tyr	Trp	Ser	_	Val	Lys	Ala	Glu		Ser	Glu	Lys	Val		Leu
_		_	5	565		_	_	_	570					575	
Arg	Ile	Ser	Val	Thr	GIN	Pro	Asp		Ile	Val	GTĀ	He		Аца	Val
.	7	C	580	3	T	14-h	3	585	C	3	3	T1-	590	Mat	~ 3
двр	гув	595	Val	ABN	Leu	Met	600	ATA	ser	ASN	Asp	605	THE	riec	GIU
an Aan	Val		His	Gln	T.a.ı	Glu		ጥም	λan	ጥኮሎ	Glv		ጥህን፦	T.eu	Glv
	610	Val	11113	GLU	LCU	615	Licu	-72-	Pott	****	620	-1-	-1-		CLJ
Met.		Met.	Asn	Ser	Phe		Va1	Phe	Gln	Glu		Glv	Leu	· Tro	Val
625					630					635	-1-				640
	Thr	qzA	Ala	Asn		Thr	Lvs	geA	Tvr		asA	Gly	Val	Tyr	
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Asn	Ala	Glu	Tyr	Ala	Glu	Arg	Phe	Met	Glu	Glu	Asn	Glu	Gly	His	Ile
			660			_		665					670		
Val	qeA	Ile	His	Asp	Phe	Ser	Leu	Gly	Ser	Ser	Pro	His	Val	Arg	Lys
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	690					695					700				
[le	Tyr	Gln	Glu	Phe	Glu	Val	Thr	Val	Pro	Asp	Ser	Ile	Thr	Ser	Trp
705					710					715					720
/al	Ala	Thr	Gly	Phe	Val	Ile	Ser	Glu	Asp	Leu	Gly	Leu	Gly	Leu	Thr
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Phr	ጥኮ፦	Pro	Va1	Glin	T_011	Gln	Δla	Phe	Gln	Dro	Phe	Phe	Tle	Dhe	וים ז

			740					745					750		
Asn	Leu	Pro	Tyr	Ser	Val	Ile	Arg	Gly	Glu	Glu	Phe	Ala	Leu	Glu	Ile
		755					760					765			
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785					790					795					800
Ala	Thr	Gly	His	Gln	Gln	Thr	Leu	Leu	Val	Pro	Ser	Glu	Asp	Gly	Ala
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	850					855					860				
	Leu	Asp	Leu	Thr		Asn	Arg	Leu	Gln		Thr	Leu	Lys	Thr	
865	_,	_		_	870	_		· ·		875	_		_		880
Ser	Phe	Ser	Pne		Pro	Asn	Thr	Val	Thr	GIÀ	Ser	Glu	Arg		Gln
~1 ~	m\	21-	~1.	885	•	•••			890		~ 7.	•	93	895	-1-
TTE	Thr	ALA		GIĄ	Asp	vaı	Leu		Pro	ser	TTE	ASN	_	rea	АТа
Com	T	T1.	900	Mot	D		a 1	905	~1	63	01 -	2	910	7 1.	3
ser	пеп	915	Arg	Mec	PLO	TŸĽ	920	сув	Gly	GIU	GIII	925	Mec	116	MSII
Dhe	215		Aen	Tla	Пет	Tla		y an	Tyr	Ton			Two	Tara	Cln
2110	930	110	711341	110	-1-	935	Deu	rsp	TYL	Dea	940	Lys	цуз	nys	GIII
Leu		Asp	Asn	Leu	Lvs		Lvs	Δla	Leu	Ser	-	Met	Ara	Gln	Glv
945		<u>-</u> -			950		_,_			955			9	J	960
	Gln	Ara	Glu	Leu		Tvr	Gln	Ara	Glu		Glv	Ser	Phe	Ser	
•				965		-4-		5	970		2			975	
Phe	Gly	Asn	Tvr		Pro	Ser	Glv	Ser	Thr	Tro	Leu	Ser	Ala	Phe	Val
	-		980	-				985		•			990		
Leu	Arg	Сув	Phe	Leu	Glu	Ala	Asp	Pro	Tyr	Ile	Asp	Ile	qeA	Gln	Asn
	-	995					1000		•		•	1005	_		
Val	Leu	His	Arg	Thr	Tyr	Thr			Lys	Gly	His			Ser	Asn
	1010		,		-	1015			-	-	1020		-		

-	Glu	Phe	Trp	Asp	Pro	Gly	Arg	Val	Ile	His	Ser	Glu	Leu	Gln	Gly
102	5				103	0				103	5				1040
Gly	Asn	Lys	Ser	Pro	Val	Thr	Leu	Thr	Ala	Tyr	Ile	Val	Thr	Ser	Leu
				104	5				105	0				105	5
Leu	Gly	Tyr	Arg	Lys	Tyr	Gln	Pro	Asn	Ile	Asp	Val	Gln	Glu	Ser	Ile
			106	0				106	5				107	0	
His	Phe	Leu	Glu	Ser	Glu	Phe	Ser	Arg	Gly	Ile	Ser	Asp	Asn	Tyr	Thr
		107	5				1086)				108	5		
Leu	Ala	Leu	Ile	Thr	Tyr	Ala	Leu	Ser	Ser	Val	Gly	Ser	Pro	Lys	Ala
	109	0				1095	5				110	0			
Lys	Glu	Ala	Leu	Asn	Met	Leu	Thr	Trp	Arg	Ala	Glu	Gln	Glu	Gly	Gly
110	5				1110)				1115	5				1120
Met	Gln	Phe	Trp	Val	Ser	Ser	Glu	Ser	Lys	Leu	Ser	Asp	Ser	Trp	Gln
				1125	5				1130)				113	5
Pro	Arg	Ser	Leu	Asp	Ile	Glu	Val	Ala	Ala	Tyr	Ala	Leu	Leu	Ser	His
	•		1140)				1145	5				1150	0	
Phe	Leu	Gln	Phe	Gln	Thr	Ser	Glu	Gly	Ile	Pro	Ile	Met	Arg	Trp	Leu
		1155	5				1160)				1165	5		
Ser	Arg	Gln	Arg	Asn	Ser	Leu	Gly	Gly	Phe	Ala	Ser	Thr	Gln	Asp	Thr
		^				1175	i				1180)			
	1170	U													
Thr	1170 Val		Leu	Lys	Ala	Leu	Ser	Glu	Phe	Ala	Ala	Leu	Met	Asn	Thr
Thr 118	Val		Leu	Lys	Ala 1190		Ser	Glu	Phe	Ala 1195		Leu	Met	Asn	1200
118	Val	Ala		_	1190)				1195	5				1200
118	Val	Ala		_	1190 Gln)				1195 Gly	5				1200 Ser
1189 Glu	Val	Ala Thr	Asn	Ile 1205	1190 Gln	Val	Thr	Val	Thr 1210	1195 Gly	Pro	Ser	Ser	Pro 1215	1200 Ser
1189 Glu	Val 5 Arg	Ala Thr	Asn	Ile 1205 Leu	1190 Gln	Val	Thr	Val	Thr 1210 Asn	1195 Gly	Pro	Ser	Ser	Pro 1215 Gln	1200 Ser
1189 Glu Pro	Val 5 Arg	Ala Thr Lys	Asn Phe 1220	Ile 1205 Leu	1190 Gln i	Val Asp	Thr Thr	Val His 1225	Thr 1210 Asn	1195 Gly) Arg	Pro Leu	Ser Leu	Ser Leu 1230	Pro 1215 Gln	1200 Ser i
1189 Glu Pro	Val 5 Arg Val	Ala Thr Lys	Asn Phe 1220 Ala	Ile 1205 Leu	1190 Gln i	Val Asp	Thr Thr	Val His 1225 Thr	Thr 1210 Asn	1195 Gly) Arg	Pro Leu	Ser Leu	Ser Leu 1230 Ser	Pro 1215 Gln	1200 Ser i
1189 Glu Pro	Val 5 Arg Val	Ala Thr Lys Leu 1235	Asn Phe 1220 Ala	Ile 1205 Leu Val	1190 Gln Ile Val	Val Asp Gln	Thr Thr Pro 1240	Val His 1225 Thr	Thr 1210 Asn Ala	1195 Gly) Arg Val	Pro Leu Asn	Ser Leu Ile 1245	Ser Leu 1230 Ser	Pro 1215 Gln) Ala	1200 Ser Thr
1189 Glu Pro	Val Arg Val Glu	Thr Lys Leu 1235	Asn Phe 1220 Ala	Ile 1205 Leu Val	1190 Gln Ile Val	Val Asp Gln	Thr Thr Pro 1240 Gln	Val His 1225 Thr	Thr 1210 Asn Ala	1195 Gly) Arg Val	Pro Leu Asn	Ser Leu Ile 1245 Tyr	Ser Leu 1230 Ser	Pro 1215 Gln) Ala	1200 Ser Thr
1189 Glu Pro Ala Gly	Val Arg Val Glu Phe	Thr Lys Leu 1235 Gly	Asn Phe 1220 Ala Phe	Ile 1205 Leu Val	Ile Gln Ile Val	Val Asp Gln Cys 1255	Thr Thr Pro 1240 Gln	Val His 1225 Thr Leu	Thr 1210 Asn Ala Asn	1195 Gly Arg Val	Pro Leu Asn Val 1260	Ser Leu Ile 1245 Tyr	Ser Leu 1230 Ser Ser	Pro 1215 Gln) Ala Val	1200 Ser Thr Asn
1189 Glu Pro Ala Gly	Val Arg Val Glu Phe 1250 Ser	Thr Lys Leu 1235 Gly	Asn Phe 1220 Ala Phe	Ile 1205 Leu Val Ala Ser	Ile Gln Ile Val	Val Asp Gln Cys 1255 Arg	Thr Thr Pro 1240 Gln	Val His 1225 Thr Leu	Thr 1210 Asn Ala Asn	1195 Gly Arg Val	Pro Leu Asn Val 1260 Gln	Ser Leu Ile 1245 Tyr	Ser Leu 1230 Ser Ser	Pro 1215 Gln) Ala Val	1200 Ser Thr Asn
Glu Pro Ala Gly Ala 1269	Val Arg Val Glu Phe 1250 Ser	Ala Thr Lys Leu 1235 Gly Gly	Asn Phe 1220 Ala Phe Ser	Ile 1205 Leu Val Ala Ser	Ile Val Ile Arg	Val Asp Gln Cys 1255 Arg	Thr Pro 1240 Gln	Val His 1225 Thr Leu Arg	Thr 1210 Asn Ala Asn Ser	1195 Gly Arg Val Val Ile 1275	Pro Leu Asn Val 1260 Gln	Ser Leu Ile 1245 Tyr Asn	Ser Leu 1230 Ser Asn Gln	Pro 1215 Gln) Ala Val Glu	1200 Ser Thr Asn Lys Ala 1280
Glu Pro Ala Gly Ala 1269	Val Arg Val Glu Phe 1250 Ser	Ala Thr Lys Leu 1235 Gly Gly	Asn Phe 1220 Ala Phe Ser	Ile 1205 Leu Val Ala Ser	1190 Gln i Ile Val Ile Arg 1270	Val Asp Gln Cys 1255 Arg	Thr Pro 1240 Gln	Val His 1225 Thr Leu Arg	Thr 1210 Asn Ala Asn Ser	1195 Gly Arg Val Val Ile 1275 Lys	Pro Leu Asn Val 1260 Gln	Ser Leu Ile 1245 Tyr Asn	Ser Leu 1230 Ser Asn Gln	Pro 1215 Gln) Ala Val Glu	1200 Ser Thr Asn Lys Ala 1280 His

			130	0				130	5				131	0	
Met	Ala	Leu	Met	Glu	Val	Asn	Leu	Leu	Ser	Gly	Phe	Met	Val	Pro	Ser
		131	5				132	0				132	5		
Glu	Ala	Ile	Ser	Leu	Ser	Glu	Thr	Val	Lys	Lys	Val	Glu	Tyr	Asp	His
	133	0				133	5				134	0			
Gly	Lys	Leu	Asn	Leu	Tyr	Leu	Asp	Ser	Val	Asn	Glu	Thr	Gln	Phe	Суз
134	5				135	0				135	5				1360
Val	Asn	Ile	Pro	Ala	Val	Arg	Asn	Phe	Lys	Val	Ser	Asn	Thr	Gln	Asp
				136	5				137	0				137	5
Ala	Ser	Val	Ser	Ile	Val	Asp	Tyr	Tyr	Glu	Pro	Arg	Arg	Gln	Ala	Val
			138	0				138	5				139	0	•
Arg	Ser	Tyr	Asn	Ser	Glu	Val	Lys	Leu	Ser	Ser	Сув	Asp	Leu	Сув	Ser
		139	5				140	0				140	5		
Asp	Val	Gln	Gly	Cys	Arg	Pro	Cys	Glu	Asp	Gly	Ala	Ser	Gly	Ser	His
	141	0				1415	5				142	0			
His	His	Ser	Ser	Val	Ile	Phe	Ile	Phe	Суз	Phe	Lys	Leu	Leu	Tyr	Phe
142	5				143	0				143	5				1440
Met	Glu	Leu	Trp	Leu											
				144	5										
	0> 3														
	1> 58														
	2> PI -														
	3> Ho		sapie	ens											
	0> 32 				_								_		_
	Phe	Pro	Ala	_	Pro	Pro	Ser	His		Leu	Leu	Arg	Leu		Leu
1			_	5	_				10	-		_		15	
Leu	GIN	Leu		Leu	Leu	Val	Val	Gln	Ala	Val	Gly	Arg	_	Leu	GIĀ
•			20		-1		_	25		_			30	~ 3	•
Arg	ALA		PTO	ATG	GIŸ	GŢĀ		Leu	GLu	Asp	Val		ITe	GIU	Arg
	*** -	35	D	•			40			3	-	45	a 1	•	n .
TÄL		TTG	PIO	Arg	YTØ	_	rro	Arg	GIU	vaI		met	σтλ	Asp	rne
T257	50	(The seco	tri ~	m	7	55	mb	Db-	~ 1	N	60	T	T	Dha	N are
65	ALY	TÅT	uta	TÅT	ASN 70	GTĀ	THE	Phe	aT.f.	75	атХ	чХ≈	nys	FIIC	ASP 80
~~					, ,					, ,					

Ser	Ser	Tyr	Asp	Arg	Asn	Thr	Leu	Val	Ala	Ile	Val	Val	Gly	Val	Gl
				85					90					95	
Arg	Leu	Ile	Thr	Gly	Met	qaA	Arg	Gly	Leu	Met	Gly	Met	Сув	Val	Asr
			100					105					110		
Glu	Arg	Arg	Arg	Leu	Ile	Val	Pro	Pro	His	Leu	Gly	Tyr	Gly	Ser	Ile
		115					120					125			
Gly	Leu	Ala	Gly	Leu	Ile	Pro	Pro	qeA	Ala	Thr	Leu	Tyr	Phe	Asp	Val
	130			•		135					140				
Val	Leu	Leu	Asp	Val	Trp	Asn	TÀS	Glu	qaA	Thr	Val	Gln	Val	Ser	Thr
145					150					155					160
Leu	Leu	Arg	Pro	Pro	His	Суз	Pro	Arg	Met	Val	Gln	Asp	Gly	Asp	Phe
				165					170					175	
Val	Arg	Tyr	His	Tyr	Asn	Gly	Thr	Leu	Leu	Asp	Gly	Thr	Ser	Phe	Asp
			180					185					190		
Thr	Ser	Tyr	Ser	Lys	Gly	Gly	Thr	Tyr	Asp	Thr	Tyr	Val	Gly	Ser	Gly
		195					200					205			
Trp	Leu	Ile	Lys	Gly	Met	Asp	Gln	Gly	Leu	Leu	Gly	Met	Суз	Pro	Gly
	210					215					220				
Glu	Arg	Arg	Lys	Ile	Ile	Ile	Pro	Pro	Phe	Leu	Ala	Tyr	Gly	Glu	Lys
225					230					235					240
Gly	Tyr	Gly	Thr	Val	Ile	Pro	Pro	Gln	Ala	Ser	Leu	Val	Phe	His	Val
				245					250					255	
Leu	Leu	Ile	Asp	Val	His	Asn	Pro	Lys	Asp	Ala	Val	Gln	Leu	Glu	Thr
			260			·		265					270		
Leu	Glu	Leu	Pro	Pro	Gly	Сув	Val	Arg	Arg	Ala	Gly	Ala	Gly	Asp	Phe
		275					280					285			
Met	Arg	Tyr	His	Tyr	Asn	Gly	Ser	Leu	Met	qaA	Gly	Thr	Leu	Phe	Asp
	290					295					300				
Ser	Ser	Tyr	Ser	Arg	Asn	His	Thr	Tyr	Asn	Thr	Tyr	Ile	Gly	Gln	Gly
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Tyr	Ile	Ile	Pro	Gly	Met	Asp	Gln	Gly	Leu	Gln	Gly	Ala	Суз	Met	Gly
				325					330					335	
Glu	Arg	Arg	Arg	Ile	Thr	Ile	Pro	Pro	His	Leu	Ala	Tyr	Gly	Glu	Asn
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Gly	Thr	Gly	Asp	Lys	Ile	Pro	Gly	Ser	Ala	Val	Leu	Ile	Phe	Asn	Val

WO 00/29448 PCT/JP99/06412

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		355					360					365			
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Leu	Ser	Arg	Pro	Ser	Glu	Thr	Суз	Asn	Glu	Thr	Thr	Lys	Leu	Gly	Asp
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Phe	Val	Arg	Tyr	His	Tyr	Asn	Cys	Ser	Leu	Leu	Asp	Gly	Thr	Gln	Leu
				405					410					415	
Phe	Thr	Ser	His	Asp	Tyr	Gly	Ala	Pro	Gln	Glu	Ala	Thr	Leu	Gly	Ala
			420					425					430		
Asn	Lys	Val	Ile	Glu	Gly	Leu	Asp	Thr	Gly	Leu	Gln	Gly	Met	Сув	Val
		435					440		:			445			
Gly	Glu	Arg	Arg	Gln	Leu	Ile	Val	Pro	Pro	His	Leu	Ala	His	Gly	Glu
	450					455					460				
Ser	Gly	Ala	Arg	Gly	Val	Pro	Gly	Ser	Ala	Val	Leu	Leu	Phe	Glu	Val
465					470					475					480
Glu	Leu	Val	Ser	Arg	Glu	Asp	Gly	Leu	Pro	Thr	Gly	Tyr	Leu	Phe	Val
				485					490					495	
Trp	His	Lys	qeA	Pro	Pro	Ala	Asn	Leu	Phe	Glu	qeA	Met	qeA	Leu	Asn
			500					505					510		
Lys	Asp	Gly	Glu	Val	Pro	Pro	Glu	Glu	Phe	Ser	Thr	Phe	Ile	Lys	Ala
		515					520					525			
Gln	Val	Ser	Glu	Gly	Lys	Gly	Arg	Leu	Met	Pro	Gly	Gln	Asp	Pro	Glu
	530					535					540				
Lys	Thr	Ile	Gly	qaA	Met	Phe	Gln	neA	Gln	Asp	Arg	Asn	Gln	Asp	Gly
545					550					555					560
Lys	Ile	Thr	Val	Asp	Glu	Leu	Lys	Leu	Lys	Ser	Asp	Glu	Asp	Glu	Glu
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Arg	Val	His	Glu	Glu	Leu										
			580												

<210> 33 <211> 410 <212> PRT <213> Homo sapiens

<400> 33

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Arg	Leu	Pro	Gly	Asp	Cys	Phe	Leu	Leu	Leu	Val	Leu	Leu	Leu	Tyr	Al
			20					25					30		
Pro	Val	Gly	Phe	Сув	Leu	Leu	Val	Leu	Arg	Leu	Phe	Leu	Gly	Ile	His
		35					40					45			
Val	Phe	Leu	Val	Ser	Сув	Ala	Leu	Pro	Asp	Ser	Val	Leu	Arg	Arg	Phe
	50					55					60				
Val	Val	Arg	Thr	Met	Cys	Ala	Val	Leu	Gly	Leu	Val	Ala	Arg	Gln	Glı
65					70					75					80
Asp	Ser	Gly	Leu	Arg	Asp	His	Ser	Val	Arg	Val	Leu	Ile	Ser	Asn	His
				85					90					95	
Val	Thr	Pro	Phe	Asp	His	Asn	Ile	Val	Asn	Leu	Leu	Thr	Thr	Суз	Ser
			100					105					110		
Thr	Pro	Leu	Leu	Asn	Ser	Pro	Pro	Ser	Phe	Val	Сув	Trp	Ser	Arg	Gl
		115					120					125			
Phe	Met	Glu	Met	Asn	Gly	Arg	Gly	Glu	Leu	Val	Glu	Ser	Leu	Lys	Arg
	130					135					140				
Phe	Сув	Ala	Ser	Thr	Arg	Leu	Pro	Pro	Thr	Pro	Leu	Leu	Leu	Phe	Pro
145					150					155					160
Glu	Glu	Glu	Ala	Thr	Asn	Gly	Arg	Glu	Gly	Leu	Leu	Arg	Phe	Ser	Ser
				165					170					175	
Trp	Pro	Phe	Ser	Ile	Gln	qeA	Val	Val	Gln	Pro	Leu	Thr	Leu	Gln	Va]
			180		•			185					190		
Gln	Arg	Pro	Leu	Val	Ser	Val	Thr	Val	Ser	Asp	Ala	Ser	Trp	Val	Ser
		195					200					205			
Glu	Leu	Leu	Trp	Ser	Leu	Phe	Val	Pro	Phe	Thr	Val	Tyr	Gln	Val	Arg
	210					215					220				
Trp	Leu	Arg	Pro	Val	His	Arg	Gln	Leu	Gly	Glu	Ala	Asn	Glu	Glu	Phe
225					230					235					240
Ala	Leu	Arg	Val	Gln	Gln	Leu	Val	Ala	Lys	Glu	Leu	Gly	Gln	Thr	Gly
				245					250					255	
Thr	Arg	Leu	Thr	Pro	Ala	Asp	Lys	Ala	Glu	His	Met	Lys	Arg	Gln	Arg
			260					265					270		
17 i a	D~~	7~~	T 013	7~~	Dec	C1=	502	212	Gln	Sor	Sar	Dha	Dwo	Dro	Sor

		275					280					285			
Pro	Gly	Pro	Ser	Pro	Asp	Val	Gln	Leu	Ala	Thr	Leu	Ala	Gln	Arg	Va]
	290					295					300				
Lys	Glu	Val	Leu	Pro	His	Val	Pro	Leu	Gly	Val	Ile	Gln	Arg	Asp	Leu
305					310					315					320
Ala	Lys	Thr	Gly	Суз	Val	Asp	Leu	Thr	Ile	Thr	Asn	Leu	Leu	Glu	Gly
				325					330					335	
Ala	Val	Ala	Phe	Met	Pro	Glu	Asp	Ile	Thr	Lys	Gly	Thr	Gln	Ser	Leu
			340					345					350		
Pro	Thr	Ala	Ser	Ala	Ser	Lys	Phe	Pro	Ser	Ser	Gly	Pro	Val	Thr	Pro
		355					360					365			
Gln	Pro	Thr	Ala	Leu	Thr	Phe	Ala	Lys	Ser	Ser	Trp	Ala	Arg	Gln	Glu
	370					375					380				
Ser	Leu	Gln	Glu	Arg	Lys	Gln	Ala	Leu	Tyr	Glu	Tyr	Ala	Arg	Arg	Arg
385					390					395					400
Phe	Thr	Glu	Arg	Arg	Ala	Gln	Glu	Ala	qaA						
				405					410						
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<21	2> PI	RT													
<21:	3> Ho	e ome	apie	ens											
	0> 34														
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Val	Leu	Leu	Val	Leu	Cys	Gly	Leu	Leu	Glu	Ala	Ser	Gly	_	Gly	Arg
			20					25					30		
Ala	Leu	Pro	Gln	Leu	Ser	Asp	Asp	Ile	Pro	Phe	Arg	Val	Asn	Trp	Pro
		35					40					45			
Gly	Thr	Glu	Phe	Ser	Leu	Pro	Thr	Thr	Gly	Val	Leu	Tyr	Lys	Glu	Asp
	50					55					60				
Asn	Tyr	Val	Ile	Met	Thr	Thr	Ala	His	Lys	Glu	Lys	Tyr	ГÀЗ	Cys	Ile
65					70					75					80
Leu	Pro	Leu	Val	Thr	Ser	Gly	qaA	Glu	Glu	Glu	Glu	Lys	Asp	Tyr	Lys
				85					90					95	

Gly	Pro	Asn	Pro	Arg	Glu	Leu	Leu	Glu	Pro	Leu	Phe	Lys	Gln	Ser	Sei
			100					105					110		
Cys	Ser	Tyr	Arg	Ile	Glu	Ser	Tyr	Trp	Thr	Tyr	Glu	Val	Суз	His	Gly
		115					120					125			
Lys	His	Ile	Arg	Gln	Tyr	His	Glu	Glu	Lys	Glu	Thr	Gly	Gln	Lys	Ile
	130					135					140				
Asn	Ile	His	Glu	Tyr	Tyr	Leu	Gly	Asn	Met	Leu	Ala	Lys	Asn	Leu	Leu
145					150					155					160
Phe	Glu	Lys	Glu	Arg	Glu	Ala	Glu	Glu	Lys	Glu	Lys	Ser	Asn	Glu	Ile
				165					170					175	
Pro	Thr	Lys	Asn	Ile	Glu	Gly	Gln	Met	Thr	Pro	Tyr	Tyr	Pro	Val	Gly
			180					185					190		
Met	Gly	Asn	Gly	Thr	Pro	Cys	Ser	Leu	Lys	Gln	Asn	Arg	Pro	Arg	Ser
		195					200					205			
Ser	Thr	Val	Met	Tyr	Ile	Суз	His	Pro	Glu	Ser	Lys	His	Glu	Ile	Leu
	210					215					220				
Ser	Val	Ala	Glu	Val	Thr	Thr	Cys	Glu	Tyr	Glu	Val	Val	Ile	Leu	Thr
225					230					235					240
Pro	Leu	Leu	Cys	Ser	His	Pro	Lys	Tyr	Arg	Phe	Arg	Ala	Ser	Pro	Val
				245					250					255	
Asn	Asp	Ile	Phe	Cys	Gln	Ser	Leu	Pro	Gly	Ser	Pro	Phe	Lys	Pro	Leu
			260					265					270		
Thr	Leu	Arg	Gln	Leu	Glu	Gln	Gln	Glu	Glu	Ile	Leu	Arg	Val	Pro	Phe
		275					280					285			
Arg	Arg	Asn	Lys	Glu	Glu	qaA	Leu	Gln	Ser	Thr	Lys	Glu	Glu	Arg	Phe
	290					295					300				
Pro	Ala	Ile	His	Lys	Ser	Ile	Ala	Ile	Gly	Ser	Gln	Pro	Val	Leu	Thr
305					310					315					320
Val	Gly	Thr	Thr	His	Ile	Ser	Lys	Leu	Thr	Asp	qeA	Gln	Leu	Ile	Lys
				325					330					335	
Glu	Phe	Leu	Ser	Gly	Ser	Tyr	Cys	Phe	Arg	Gly	Gly	Val	Gly	Trp	Trp
			340					345					350		
Lys	Tyr	Glu	Phe	Сув	Tyr	Gly	Lys	His	Val	His	Gln	Tyr	His	Glu	Asp
		355					360					365			
Tvs	GRA	Ser	Glv	Lvs	Thr	Ser	Val	۷al	Val	Glv	Thr	Tro	Asn	Gln	Glu

370		375		380	
Glu His Ile	Glu Trp A	la Lys Lys	Asn Thr Ala	Arg Ala Tyr	His Leu
385	3	90	395		400
Gln Asp Asp	Gly Thr G	ln Thr Val	Arg Met Val	Ser His Phe	Tyr Gly
	405	•	410		415
Asn Gly Asp	Ile Cys A	sp Ile Thr	Asp Lys Pro	Arg Gln Val	Thr Val
	420		425	430	•
Lys Leu Lys	Cys Lys G	lu Ser Asp	Ser Pro His	Ala Val Thr	Val Tyr
435		440		445	
Met Leu Glu	Pro His S	er Cys Gln	Tyr Ile Leu	Gly Val Glu	Ser Pro
450		455		460	
Val Ile Cys	Lys Ile L	eu Asp Thr	Ala Asp Glu	Asn Gly Leu	Leu Ser
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Leu Pro Asn					
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Gln Leu Arg	Asn Val A	a Leu Leu	Ala Leu Pro	Arg Val Leu	Leu Pro
	20		25	30	
Leu His Phe	Leu Leu Pr	o Ile Phe	Leu Ala Ala	Val Pro Ala	His Arg
35		40		45	
Cys Ala Leu	Pro Gly Al	a Pro Ala	Asn Phe Ser	His Gln Asp	Val Trp
50		55		60	
Leu Glu Ala	His Leu Pr	o Arg Glu	Pro Asp Gly	Thr Leu Ser	Ser Cys
65	7	0	75		80
Leu Arg Phe	Ala Tyr Pr	o Gln Ala	Leu Pro Asn	Thr Thr Leu	Gly Glu
	85		90		95
Glu Arg Gln	Ser Arg Gl	y Glu Leu	Glu Asp Glu	Pro Ala Thr	Val Pro
	100		105	110	

105

Сув	Ser	Gln	Gly	Trp	Glu	Tyr	qaA	His	Ser	Glu	Phe	Ser	Ser	Thr	Ile
		115					120					125			
Ala	Thr	Glu	Ser	Gln	Val	Gly	Ile	Tyr	Ile	Ile	His	Leu	Glu	Val	Gl
	130					135					140				-
Сув	Arg	Trp	Arg	Gln	Ser	Pro	Trp	Glu	Ala	Ala	Gly	Arg	Gly	Leu	Pro
145					150					155					160
Trp	Glu	Glu	Ala	Glu	Ala	Ala	Gly	Leu	Gly	Arg	Asp	Lys	Val	Ser	Туз
				165					170					175	
Ser	Pro	Ser	Trp	Arg	Glu	Ser	Leu	Gly	Gly	Leu	Leu	Ser	Gly	Met	Glu
			180					185					190		
Trp	Asp	Leu	Val	Сув	Glu	Gln	Lys	Gly	Leu	Asn	Arg	Ala	Ala	Ser	Thi
		195					200					205			
Phe	Phe	Phe	Ala	Gly	Val	Leu	Val	Gly	Ala	Val	Ala	Phe	Gly	Tyr	Leu
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T.eu		Glv	เลา	עדעש	T.e.11		T.e.11	Pro	Taya	Leu		ጥሆነተ	Glv	Glv	Tle
545		1	• •		550	502	200			555		-1-	1	,	560
	T 011	T 011	31 -	210		mb	810	Tou	Tou	Leu	Dro	Clu	mh∽	7 20	
ALG	Leu	Leu	Ara		GTĂ	TILL	ALG	reu		Leu	PIG	GIU	1111		GIII
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63/233

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Val		ITE	Thr	Val	Thr	Gln	Arg	Asn	Tyr	Thr		TÄL	drr.	ser	GTĀ	
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	V 04.4.		U	425	421	****	- 1	2,0	430	uzu		210		435		
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Val	Gly	Arg	Gly	Leu	Gly	Arg	Ala	Ser	Pro	Ala	Gly	Gly	Pro	Leu	Glu	
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Ile	Val	Val	Gly	Val	Gly	Arg	Leu	Ile	Thr	Gly	Met	Asp	Arg	Gly	Leu	
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Met	Gly	Met	Суз	Val	Asn	Glu	Arg	Arg	Arg	Leu	Ile	Val	Pro	Pro	His	
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Leu	Gly	Tyr	Gly	Ser	Ile	Gly	Leu	Ala	Gly	Leu	Ile	Pro	Pro	Asp	Ala	
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Thr	Leu	Tyr	Phe	Asp	Val	Val	Leu	Leu	qaA	Val	Trp	Asn	ГЛЗ	Glu	Asp	
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Thr	Val	Gln	Val	Ser	Thr	Leu	Leu	Arg	Pro	Pro	His	Сув	Pro	Arg	Met	
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Ser	Leu	Val	Phe	His	Val	Leu	Leu	Tle	asa	Val	His	Asn	Pro	Lvs	asa	

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Ala	Val	Gln	Leu	Glu	Thr	Leu	Glu	Leu	Pro	Pro	Gly	Суз	Val	Arg	Arg	
	•		270					275					280			
gcc	ggg	gcc	aaa	gac	ttc	atg	ege	tac	cac	tac	aat	ggc	tcc	ttg	atg	975
Ala	Gly	Ala	Gly	Asp	Phe	Met	Arg	Tyr	His	Tyr	Asn	Gly	Ser	Leu	Met	
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Thr	Tyr	Ile	Gly	Gln	Gly	Tyr	Ile	Ile	Pro	Gly	Met	qeA	Gln	Gly	Leu	
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Gln	Gly	Ala	Сув	Met	Gly	Glu	Arg	Arg	Arg	Ile	Thr	Ile	Pro	Pro	His	
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ctc	gcc	tat	ggg	gag	aat	gga	act	gga	gac	aag	atc	cct	ggc	tct	gcc	1167
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Val	Leu	Ile	Phe	Asn	Val	His	Val	Ile	Asp	Phe	His	Asn	Pro	Ala	Asp	
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Val	Val	Glu	Ile	Arg	Thr	Leu	Ser	Arg	Pro	Ser	Glu	Thr	Сув	Asn	Glu	
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Thr	Thr	Lys	Leu	Gly	Asp	Phe	Val	Arg	Tyr	His	Tyr	Asn	Cys	Ser	Leu	
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31u	Ala	Thr	Leu	Gly	Ala	Asn	Lys	Val	Ile	Glu	Gly	Leu	qeA	Thr	Gly	
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~+~	000	~~~	ata	tat	at a	aas	and a	200	000	222	ata	ata	at a	000	000	1.455

Leu Gln Gly Met Cys Val Gly Glu Arg Arg Gln Leu Ile Val Pro Pro	
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His Leu Ala His Gly Glu Ser Gly Ala Arg Gly Val Pro Gly Ser Ala	
460 465 470	
gtg ctg ctg ttt gag gtg gag ctg gtg tcc cgg gag gat ggg ctg ccc	1551
Val Leu Leu Phe Glu Val Glu Leu Val Ser Arg Glu Asp Gly Leu Pro	
475 480 485 490	
aca ggc tac ctg ttt gtg tgg cac aag gac cct cct gcc aac ctg ttt	1599
Thr Gly Tyr Leu Phe Val Trp His Lys Asp Pro Pro Ala Asn Leu Phe	
495 500 505	
gaa gac atg gac ctc aac aag gat ggc gag gtc cct ceg gag gag ttc	1647
Glu Asp Met Asp Leu Asn Lys Asp Gly Glu Val Pro Pro Glu Glu Phe	
510 515 520	1 605
tcc acc ttc atc aag gct caa gtg agt gag ggc aaa gga cgc ctc atg Ser Thr Phe Ile Lys Ala Gln Val Ser Glu Gly Lys Gly Arg Leu Met	1695
525 530 535	
cet ggg cag gae cet gag aaa ace ata gga gae atg tte cag aac cag	1743
Pro Gly Gln Asp Pro Glu Lys Thr Ile Gly Asp Met Phe Gln Asn Gln	1/43
540 545 550	
gac ege aac eag gac gge aag ate aca gte gac gag ete aag etg aag	1791
Asp Arg Asn Gln Asp Gly Lys Ile Thr Val Asp Glu Leu Lys Leu Lys	
555 560 565 570	
tca gat gag gac gag gag egg gtc cac gag gag etc tga ggggcaggga	1840
Ser Asp Glu Asp Glu Glu Arg Val His Glu Glu Leu	
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ageoctacet eteccatgee etttgecete etecetegee tecagtggag getgagetga	2380

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ccd dad cdd		-	_									160
Pro Glu Arg	Leu P	he Asp		lis A	rg Leu	Pro		Asp	Сув	Phe	Leu	
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Leu Leu Val	Leu L		Tyr P	Ala P	ro Val		Phe	СЛа	Leu	Leu		
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Leu Arg Leu		_	Ile F	lis V		Leu	Val	Ser	Сув		Leu	
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cca gac ago	-	_			_	-		_	_	-		304
Pro Asp Ser		eu Arg	Arg E			Arg	Thr	Met	_	Ala	Val	
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cta ggg ctc												352
Leu Gly Leu		ıa Arg	Gln G		sp Ser	GŢĀ	Leu	-	Asp	His	ser	
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Val Arg Val	Leu I	le Ser	Asn F	lis V	al Thr	Pro	Phe	Asp	His	Asn	Ile	

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Val	Asn	Leu	Leu	Thr	Thr	Сув	Ser	Thr	Pro	Leu	Leu	Asn	Ser	Pro	Pro			
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Ser	Phe	Val	Cys	Trp	Ser	Arg	Gly	Phe	Met	Glu	Met	Asn	Gly	Arg	Gly			
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Glu	Leu	Val	Glu	Ser	Leu	Lys	Arg	Phe	Сув	Ala	Ser	Thr	Arg	Leu	Pro			
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Pro	Thr	Pro	Leu	Leu	Leu	Phe	Pro	Glu	Glu	Glu	Ala	Thr	Asn	Gly	Arg			
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Val	Gln	Pro	Leu	Thr	Leu	Gln	Val	Gln	Arg	Pro	Leu	Val	Ser	Val	Thr			
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gtg	tca	gat	gcc	tcc	tgg	gtc	tca	gaa	ctg	ctg	tgg	tca	ctt	ttc	gtc	•	736	
Val	Ser	Asp	Ala	Ser	Trp	Val	Ser	Glu	Leu	Leu	Trp	Ser	Leu	Phe	Val			
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cct	ttc	acg	gtg	tat	caa	gta	agg	tgg	ctt	cgt	cct	gtt	cat	cgc	caa	•	784	
Pro	Phe	Thr	Val	Tyr	Gln	Val	Arg	Trp	Leu	Arg	Pro	Val	His	Arg	Gln			
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cta	999	gaa	gcg	aat	gag	gag	ttt	gca	ctc	cgt	gta	caa	cag	ctg	gtg	8	832	
Leu	Gly	Glu	Ala	Asn	Glu	Glu	Phe	Ala	Leu	Arg	Val		Gln	Leu	Val			
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Ala	Glu	His	Met	Lys	Arg	Gln	Arg	His	Pro	Arg	Leu	Arg	Pro	Gln	Ser			
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700	~~~	+~+	tat	++~	aat	~~~	+	aat			+-+	aat	ant.	ata	990	0	176	

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Leu	Gly	Val	Ile	Gln	Arg	Asp	Leu	Ala	Lys	Thr	Gly	Сув	Val	Asp	Leu	
		315					320					325				
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Thr	Ile	Thr	Asn	Leu	Leu	Glu	Gly	Ala	Val	Ala	Phe	Met	Pro	Glu	Asp	
	330					335					340				•	
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Ile	Thr	Lys	Gly	Thr	Gln	Ser	Leu	Pro	Thr	Ala	Ser	Ala	Ser	Lys	Phe	
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Pro	Ser	Ser	Gly	Pro	Val	Thr	Pro	Gln	Pro	Thr	Ala	Leu	Thr	Phe	Ala	
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aag	tct	tcc	tgg	gcc	cgg	cag	gag	agc	ctg	cag	gag	cgc	aag	caa	gca	1264
Lys	Ser	Ser	Trp	Ala	Arg	Gln	Glu	Ser	Leu	Gln	Glu	Arg	Lys	Gln	Ala	
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Ala	qaA															
	410															
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Pro	Gly	Gly	Pro	Val	Leu	Leu	Val	Leu	Cys	Gly	Leu	Leu	Glu	Ala	Ser	
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Gly	Gly	Gly	Arg	Ala	Leu	Pro	Gln	Leu	Ser	Asp	Asp	Ile	Pro	Phe	Arg	•
	30					35					40				•	
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Val	Asn	Trp	Pro	Gly	Thr	Glu	Phe	Ser	Leu	Pro	Thr	Thr	Gly	Val	Leu	
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Tyr	Lys	Glu	Asp	Asn	Tyr	Val	Ile	Met	Thr	Thr	Ala	His	Lys	Glu	Lys	
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tat	aaa	tgc	ata	ctt	ccc	ctt	gtg	aca	agt	ggg	gat	gag	gaa	gaa	gaa	292
Tyr	Lys	Cys	Ile	Leu	Pro	Leu	Val	Thr	Ser	Gly	Asp	Glu	Glu	Glu	Glu	
			80					85					90			
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Lys	Ąsp	Tyr	Lys	Gly	Pro	Asn	Pro	Arg	Glu	Leu	Leu	Glu	Pro	Leu	Phe	
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Lys	Gln	Ser	Ser	Суз	Ser	Tyr	Arg	Ile	Glu	Ser	Tyr	Trp	Thr	Tyr	Glu	
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	Суз	His	Gly	Lys	His	Ile	Arg	Gln	Tyr	His	Glu	Glu	Lys	Glu	Thr	
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Gly	Gln	Lys	Ile	Asn	Ile	His	Glu	Tyr	Tyr	Leu	Gly	Asn	Met	Leu	Ala	
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Lys	Asn	Leu	Leu	Phe	Glu	Lys	Glu	Arg	Glu	Ala	Glu	Glu	Lys	Glu	Lys	
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	Val	Glu	Tyr	Glu	Cys	Thr	Thr	Val	Glu	Ala	Val	Ser	Leu	Ile	Glu	His
		235					230					225				
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	Arg	Phe	Arg	Tyr	Lys	Pro	His	Ser	Суз	Leu	Leu	Pro	Thr	Leu	Ile	Val
			250					245					240			
820	cca	tct	gga	cca	ctg	tca	caa	tgt	ttt	ata	gac	aat	gtg	cct	tet	gca
	Pro	Ser	Gly	Pro	Leu	Ser	Gln	Cya	Phe	Ile	Asp	Asn	Val	Pro	Ser	Ala
				265					260					255		
868			_	-	_	-		ctg			_				-	
	Leu	Ile	Glu	Glu	Gln	Gln	Glu	Leu	Gln	Arg	Leu	Thr	Leu	Pro	Lys	Phe
					280					275					270	
916	aaa	act	tca	caa	ttg	gat	gaa	gag	aaa	aat	aga	agg	ttt	cct	gtg	agg
	Lys	Thr	Ser	Gln	Leu	Asp	Glu	Glu	Lys	Asn	Arg	Arg	Phe	Pro	Val	Arg
	300					295					290					285
964	cag	tct	ggc	att	gct	att	tcg	aag	cac	atc	gcg	cca	ttt	aga	gag	gaa
	Gln		Gly	Ile	Ala	Ile	Ser	Lys	His	Ile	Ala	Pro	Phe	Arg	Glu	Glu
		315					310					305				
1012	-	-		_				cac				-				
	Asp	Asp	Thr	Leu	Lys	Ser	Ile	His	Thr	Thr	Gly	Val	Thr	Leu	Val	Pro
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1108	caa	cat	gta	cat	aaa	ggc	tat	tgc	tte	gaa	tat	aaa	tgg	tgg	ggt	gtc
	C1	174 ~	***	T7: ~	T	~ 1	(Th	~	Dho	~7··	m	T	M	M	<i>~</i> 1	**-7

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Trp	Asn	Gln	Glu	Glu	His	Ile	Glu	Trp	Ala	Lys	Lys	Asn	Thr	Ala	Arg	
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gct	tat	cat	ctt	caa	gac	gat	ggt	acc	cag	aca	gtc	agg	atg	gtg	tca	1252
Ala	Tyr	His	Leu	Gln	Asp	Asp	Gly	Thr	Gln	Thr	Val	Arg	Met	Val	Ser	
			400					405					410			
cat	ttt	tat	gga	aat	gga	gat	att	tgt	gat	ata	act	gac	aaa	cca	aga	1300
His	Phe	Tyr	Gly	Asn	Gly	Asp	Ile	Суз	qaA	Ile	Thr	Asp	Lys	Pro	Arg	
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cag	gtg	act	gta	aaa	cta	aag	tge	aaa	gaa	tca	gat	tca	cct	cat	gct	1348
Gln	Val	Thr	Val	Lys	Leu	Lys	Сув	Lys	Glu	Ser	Asp	Ser	Pro	His	Ala	
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Val	Thr	Val	Tyr	Met	Leu	Glu	Pro	His	Ser	Cys	Gln	Tyr	Ile	Leu	Gly	
445					450					455					460	
gtt	gaa	tct	cca	gtg	atc	tgt	aaa	atc	tta	gat	aca	gca	gat	gaa	aat	1444
Val	Glu	Ser	Pro	Val	Ile	Cys	Lys	Ile	Leu	Asp	Thr	Ala	Asp	Glu	Asn	
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Gly	Leu	Leu	Ser	Leu	Pro	Asn										
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gaaa	agat	ca t	tgaa	agto	a to	ataa	ittto	: tgt	ccca	ctg	tgto	tcat	ta t	agag	rttete	1550
agco	atto	ga c	ctct	tcte	a ag	gatg	gtat	aaa	atga	ctc	tcas	ccac	tt t	gtga	ataca	1610
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Gly Phe Gly Pro Pl	ne Gln Leu Arg Asn	Val Ala Leu Leu Ala	a Leu Pro											
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cga gtg ctg cta co	ca ctg cac ttc ctc	ctg ccc atc ttc ct	g get gee 148											
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	cg Cys Ala Leu Pro	-	n Phe Ser											
45	50	55												
	gg ctg gag gcc cat	2. 2.												
-	To Leu Glu Ala His 1	-												
60	65	70	75											
	ge ete ege ttt gee 1													
·	ys Leu Arg Phe Ala : 30	ryr pro Gin Aia Let 85	90											
	aa gaa agg cag agc (
	lu Glu Arg Gln Ser <i>l</i>	_												
95	100	105	_											
	c tgc tct cag ggc (
	o Cys Ser Gln Gly													
110	115	120												
tte tee tet ace at	t gea act gag tee o	eag gte ggt att tac	ata atc 436											
	e Ala Thr Glu Ser (
125	130	135												
cat ctg gag gtg ga	a tgt egg tgg agg o	eag tet eee tgg gag	g gca gca 484											
His Leu Glu Val Gl	u Cys Arg Trp Arg (Sin Ser Pro Trp Glu	Ala Ala											
140	145	150	155											
ggt ega gge ett ee	t tgg gaa gaa gct g	gag get gea gga etg	ggg agg 532											
	o Trp Glu Glu Ala G													
16	0 1	L65	170											

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qeA	ГЛЗ	Val	Ser	Tyr	Ser	Pro	Ser	Trp	Arg	Glu	Ser	Leu	Gly	Gly	Leu	
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Arg	Ala	Ala	Ser	Thr	Phe	Phe	Phe	Ala	Gly	Val	Leu	Val	Gly	Ala	Val	
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Val	Ala	Tyr	Val	Ser	Thr	Leu	Val	Leu	Gly	Leu	Ala	Ser	Ala	Ala	Ser	
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gtc	age	tat	gta	atg	ttt	gcc	atc	acc	ege	acc	ctt	act	ggc	tca	gcc	820
Val	Ser	Tyr	Val	Met	Phe	Ala	Ile	Thr	Arg	Thr	Leu	Thr	Gly	Ser	Ala	
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ctg	gat	ggt	ttt	acc	atc	atc	gtg	atg	cca	ctg	gag	ctg	gag	tgg	ctg	868
Leu	Ala	Gly	Phe	Thr	Ile	Ile	Val	Met	Pro	Leu	Glu	Leu	Glu	Trp	Leu	
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aca	9 99	ggc	gtg	atg	ctg	ctg	gca	ctg	gtt	ggg	tac	ctg	ata	cgg	gac	964
Thr	Gly	Gly	Val	Met	Leu	Leu	Ala	Leu	Val	Gly	Tyr	Leu	Ile	Arg	Asp	
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Trp	Arg	Trp	Leu	Leu	Leu	Ala	Val	Thr	Leu	Pro	Суз	Ala	Pro	Gly	Ile	
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ctc	agc	ctc	tgg	tgg	gtg	cct	gag	tct	gca	cgc	tgg	ctt	ctg	acc	caa	1060
Leu	Ser	Leu	Trp	Trp	Val	Pro	Glu	Ser	Ala	Arg	Trp	Leu	Leu	Thr	Gln	
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ggc	cat	gtg	aaa	gag	gcc	cac	agg	tac	ttg	ctc	cac	tgt	gcc	agg	ctc	1108
2117	uie	Val	T.ve	Glu	ald	uio	Ara	ጥህጉ	T_an	Tau	uie	Cva	a f 4	Ara	Ten	

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Asn	Gly	Arg	Pro	Val	Сув	Glu	Asp	Ser	Phe	Ser	Gln	Glu	Ala	Val	Ser	
	365					370					375					
aaa	gtg	gcc	gcc	ggg	gaa	cgg	gtg	gtc	cga	aga	cct	tca	tac	cta	gac	1204
Lys	Val	Ala	Ala	Gly	Glu	Arg	Val	Val	Arg	Arg	Pro	Ser	Tyr	Leu	qaA	
380					385					390					395	
ctg	ttc	cgc	aca	cca	cgg	ctc	cga	cac	atc	tca	ctg	tgc	tgc	gtg	gtg	1252
Leu	Phe	Arg	Thr	Pro	Arg	Leu	Arg	His	Ile	Ser	Leu	Суз	Сув	Val	Val	
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gtg	tgg	ttc	gga	gtg	aac	ttc	tee	tat	tac	ggc	ctg	agt	ctg	gat	gtg	1300
Val	Trp	Phe	Gly	Val	Asn	Phe	Ser	Tyr	Tyr	Gly	Leu	Ser	Leu	Asp	Val	
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Ser	Gly	Leu	Gly	Leu	Asn	Val	Tyr	Gln	Thr	Gln	Leu	Leu	Phe	Gly	Ala	
		430					435					440				
gtg	gaa	ctg	ccc	tcc	aag	ctg	ctg	gtc	tac	ttg	teg	gtg	cgc	tac	gca	1396
Val	Glu	Leu	Pro	Ser	Lys	Leu	Leu	Val	Tyr	Leu	Ser	Val	Arg	Tyr	Ala	
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Gly	Arg	Arg	Leu	Thr	Gln	Ala	Gly	Thr	Leu		Gly	Thr	Ala	Leu	Ala	
460					465					470					475	
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Phe	Gly	Thr	Arg		Leu	Val	Ser	Ser	Asp	Met	Lys	Ser	Trp		Thr	
				480					485					490		
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Val	Leu	Ala		Met	Gly	Lys	Ala		Ser	Glu	Ala	Ala		Thr	Thr	
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Ala	Tyr		Phe	Thr	Ser	Glu	Leu	Tyr	Pro	Thr	Val		Arg	Gln	Thr	
		510					515					520	•			
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Gly		Gly	Leu	Thr	Ala		Val	Gly	Arg	Leu		Gly	Ser	Leu	Ala	
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cca	ctg	gcg	gcc	ttg	ctg	gat	gga	gtg	tgg	ctg	tca	ctg	ccc	aag	ctt	1684

Pro Leu Ala Ala Leu Leu Asp Gly Val Trp Leu Ser Leu Pro Lys Leu	
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act tat ggg ggg atc gcc ctg ctg gct gcc ggc acc gcc ctc ctg ctg	1732
Thr Tyr Gly Gly Ile Ala Leu Leu Ala Ala Gly Thr Ala Leu Leu Leu	
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cea gag acg agg cag gca cag ctg cca gag acc atc cag gac gtg gag	1780
Pro Glu Thr Arg Gln Ala Gln Leu Pro Glu Thr Ile Gln Asp Val Glu	
575 580 585	
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Arg Lys Ser Ala Pro Thr Ser Leu Gln Glu Glu Met Pro Met Lys	•
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Gln Val Gln Asn	
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Leu Leu Ala Leu Leu Ala Arg Ala Gly Leu Arg Lys Pro Glu Ser	
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cag gag geg geg eeg tta tea gga eea tge gge ega egg gte ate aeg	149
Sin Glu Ala Ala Pro Leu Ser Gly Pro Cys Gly Arg Arg Val Ile Thr	

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Ser	Arg	Ile	Val	Gly	Gly	Glu	Asp	Ala	Glu	Leu	Gly	Arg	Trp	Pro	Trp	
40					45					50					55	
cag	ggg	ago	ctg	cgc	ctg	tgg	gat	tcc	Cac	gta	tga	gga	gtg	ago	ctg	245
Gln	Gly	Ser	Leu	Arg	Leu	Trp	Asp	Ser	His	Val	Сув	Gly	Val	Ser	Leu	
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ctc	agc	cac	cgc	tgg	gca	ctc	acg	gcg	gcg	cac	tgc	ttt	gaa	acc	tat	293
Leu	Ser	His	Arg	Trp	Ala	Leu	Thr	Ala	Ala	His	Суз	Phe	Glu	Thr	Tyr	
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Ser	Asp	Leu	Ser	Asp	Pro	Ser	Gly	Trp	Met	Val	Gln	Phe	Gly	Gln	Leu	
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Phe	Val	Ser	Asn	Ile	Tyr	Leu	Ser	Pro	Arg	Tyr	Leu	Gly	Asn	Ser	Pro	
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Tyr	Asp	Ile	Ala	Leu	Val	Lys	Leu	Ser	Ala	Pro	Val	Thr	Tyr	Thr	Lys	
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cac	atc	cag	CCC	atc	tgt	ctc	cag	gcc	tcc	aca	ttt	gag	ttt	gag	aac	533
His	Ile	Gln	Pro	Ile	Cys	Leu	Gln	Ala	Ser	Thr	Phe	Glu	Phe	Glu	Asn	
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Arg	Thr	Asp	Суз	Trp	Val	Thr	Gly	Trp	Gly	Tyr	Ile	ГÅа	Glu	Asp	Glu	
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								cag	_	_	_	-	-			629
Ala	Leu	Pro	Ser	Pro	His	Thr	Leu	Gln	Glu	Val	Gln	Val	Aļa	Ile	Ile	
	185					190					195					
			-	_				ttc		-		-		-	-	677
Asn	Asn	Ser	Met			His	Leu	Phe	Leu	Lys	Tyr	Ser	Phe	Arg	Lys	
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Asp Ala Cys Phe Gly Asp Ser Gly Gly Pro Leu Ala Cys Asn Lys Asn	
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Gly Leu Trp Tyr Gln Ile Gly Val Val Ser Trp Gly Val Gly Cys Gly	
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egg eee aat egg eee ggt gte tac ace aat ate age eae eae ttt gag	869
Arg Pro Asn Arg Pro Gly Val Tyr Thr Asn Ile Ser His His Phe Glu	
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Trp Ile Gln Lys Leu Met Ala Gln Ser Gly Met Ser Gln Pro Asp Pro	
280 285 290 295	
tee tgg eeg eta ete ttt tte eet ett ete tgg get ete eea ete etg	965
Ser Trp Pro Leu Leu Phe Phe Pro Leu Leu Trp Ala Leu Pro Leu Leu	
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cagaaaaagg cgtggaccct gccagcagcc aggcc atg gag ctc tct gat gtc	233

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Thr Leu Ile Glu Gly Val Gly Asn	Glu Val Met Val Val Ala Gly Val	·
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gtg gtg ctg att cta gcc ttg gtc	cta get tgg ete tet ace tae gta	329
Val Val Leu Ile Leu Ala Leu Val 1	Leu Ala Trp Leu Ser Thr Tyr Val	
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gca gac agc ggt agc aac cag ctc	ctg ggc gct att gtg tca gca ggc	377
Ala Asp Ser Gly Ser Asn Gln Leu	Leu Gly Ala Ile Val Ser Ala Gly	
40 45	50	
gac aca tee gte ete eac etg ggg	cat gtg gac cac ctg gtg gca ggc	425
Asp Thr Ser Val Leu His Leu Gly I	His Val Asp His Leu Val Ala Gly	
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caa ggc aac ccc gag cca act gaa d	ctc ccc cat cca tca gag gca aat	473
Gln Gly Asn Pro Glu Pro Thr Glu 1	Leu Pro His Pro Ser Glu Ala Asn	
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Thr Ser Leu Asp Lys Lys Ala Arg		
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Leu Ile Met Gln Leu Gly Ser Val Leu Leu Thr Arg Cys Pro Phe Trp	
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Gly Cys Phe Ser Gln Leu Met Leu Tyr Ala Glu Arg Ala Glu Ala Arg	
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Arg Lys Pro Asp Ile Pro Val Pro Tyr Leu Tyr Phe Asp Met Gly Ala	
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Ala Val Leu Cys Ala Ser Phe Met Ser Phe Gly Val Lys Arg Arg Trp	
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Phe Ala Leu Gly Ala Ala Leu Gln Leu Ala Ile Ser Thr Tyr Ala Ala	
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Tyr Ile Gly Gly Tyr Val His Tyr Gly Asp Trp Leu Lys Val Arg Met	
95 100 105	

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Arg	Cys	Trp	Gly	Ala	Val	Pro	Pro	Glu	Thr	Ser	Gln	Pro	Leu	Pro	Ala	
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Pro	Gly	Pro	Gly	Leu	Ser	Val	Arg	Leu	Leu	Arg	qaA	Pro	Arg	Сув	Pro	•
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Lys Leu Leu Phe Ile Val Pro Leu Val Ile Ser Ser Arg Ile Asp	
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Gln Asp Asn Ser Ser Phe Asp Ser Leu Ser Pro Glu Pro Lys Ser Arg	
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Phe Ala Met Leu Asp Asp Val Lys Ile Leu Ala Asn Gly Leu Leu Gln	
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Arg Thr Thr Tyr Lys Leu Gln Val Lys Asn Glu Glu Val Lys Asn Met	
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Ile	Gln	Asn	Gln	Pro	Glu	Thr	Pro	Glu	His	Pro	Glu	Val	Thr	Ser	Leu	
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Thr	Val	Glu	Asp	Gln	Tyr	Lys	Gln	Leu	Asn	Gln	Gln	His	Ser	Gln	Ile	
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aaa	gaa	ata	gaa	aat	cag	ctc	aga	agg	act	agt	att	caa	gaa	ccc	aca	679
Lys	Glu	Ile	Glu	Asn	Gln	Leu	Arg	Arg	Thr	Ser	Ile	Gln	Glu	Pro	Thr	
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Glu	Ile	Ser	Leu	Ser	Ser	Lys	Pro	Arg	Ala	Pro	Arg	Thr	Thr	Pro	Phe	
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Ala	Ile	Arg	Pro	Ser	Asn	Ser	Gln	Val	Phe	His	Val	Tyr	Суз	Asp	Val	
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Asn	Tyr	Thr	Leu	His	Leu	Val	Ala	Ile	Thr	Gly	Asn	Val	Pro	Asn	Ala	
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Ile	Pro	Glu	Asn	Lys	Asp	Leu	Val	Phe	Ser	Thr	Trp	qeA	His	Lys	Ala	
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Lys	Gly	His	Phe	Asn	Cys	Pro	Glu	Gly	Tyr	Ser	Gly	Gly	Trp	Trp	Trp	
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His	Asp	Glu	Суз	Gly	Glu	Asn	Asn	Leu	Asn	Gly	Lys	Tyr	Asn	Lys	Pro	
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Arg	Ala	Lys	Ser	Lys	Pro	Glu	Arg	Arg	Arg	Gly	Leu	Ser	Trp	Lys	Ser	
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Gln	Asn	Gly	Arg	Leu	Tyr	Ser	Ile	Lys	Ser	Thr	Lys	Met	Leu	Ile	His	
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Pro	Thr	qzA	Ser	Glu	Ser	Phe	Glu									
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Leu Gly Ile Lys Thr Asp Ile Thr Pro Val Ala Tyr Phe Phe Leu Thr	
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Trp Gly Leu Arg Ser Gln Leu Gln Ser Met Gln Thr Glu Ser Pro Gly	,,,
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Pro Ser Gly Asn Ala Arg Asp Asn Glu Ala Phe Glu Val Pro Val Tyr	
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Glu Glu Gln Pro Ser His Pro Glu Gly Ser Arg Arg Ala Lys Leu Glu	

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Gln Arg Arg Met Ala Ser Glu Gly Ser Met Ala Gln Glu Gly Ser Pro	
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Cva	_	Dhe	Ten	Len	Thr		- בו	T.e.11	Man-	Gly		Sor	Glv	ui e	Dhe
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Gln	Leu	Leu		Leu	Leu	Pro	Glu		Met	Ala	Glu	Lvs		Cvs	Glu
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Asn	Met	Leu	Glu	Val	Phe	Val	Ser	Ser	Leu	Glu	Glu	Phe	Gln	Pro	Asp
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Leu	Val	Val	Leu	Ser	Gly	Leu	His	Met	Met	Glu	Gly	Gln	Ser	Lys	Glu
			260					265					270		
Leu	Gln	Arg	Lys	Arg	Leu	Leu	Glu	Val	Val	Thr	Ser	Ile	Ser	Asp	Ile
		275					280					285			
Pro	Thr	Gly	Ile	Pro	Val	His	Leu	Glu	Leu	Ala	Ser	Met	Thr	Asn	Arg
	290					295					300				
Glu	Leu	Met	Ser	Ser	Ile	Val	His	Gln	Gln	Val	Phe	Pro	Ala	Val	Thr
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Ser	Leu	Gly	Leu	Asn	Glu	Gln	Glu	Leu	Leu	Phe	Leu	Thr	Gln	Ser	Ala
				325					330					335	
Ser	Gly	Pro	His	Ser	Ser	Leu	Ser	Ser	Trp	Asn	Gly	Val	Pro	Asp	Val
			340					345					350		
Gly	Met	Val	Ser	Asp	Ile	Leu	Phe	Trp	Ile	Leu	Lys	Glu	His	Gly	Arg
		355					360					365			
Ser	Lys	Ser	Arg	Ala	Ser	qzA	Leu	Thr	Arg	Ile	His	Phe	His	Thr	Leu
	370					375					380				
Val	Tyr	His	Ile	Leu	Ala	Thr	Val	qaA	Gly	His	Trp	Ala	Asn	Gln	Leu
385					390					395					400
Ala	Ala	Val	Ala	Ala	Gly	Ala	Arg	Val	Ala	Gly	Thr	Gln	Ala	Сув	Ala
				405					410					415	
Thr	Glu	Thr	Ile	Asp	Thr	Ser	Arg	Val	Ser	Leu	Arg	Ala	Pro	Gln	Glu
			420					425					430		

Ph	Met	Thr	Ser	His	Ser	Glu	Ala	Gly	Ser	Arg	Ile	Val	Leu	Asn	Pr
		435					440					445			
Asn	Lys	Pro	Val	Val	Glu	Trp	His	Arg	Glu	Gly	Ile	Ser	Phe	His	Phe
	450					455					460				
Thr	Pro	Val	Leu	Val	Суз	Lys	Asp	Pro	Ile	Arg	Thr	Val	Gly	Leu	Gl
465					470					475			÷		48
Asp	Ala	Ile	Ser	Ala	Glu	Gly	Leu	Phe	Tyr	Ser	Glu	Val	His	Pro	Hi
				485					490					495	
Tyr															
	0> 63														
	1> 4:														
	2> PI														
	3> Ho		sapi	ens											
	0> 63 -		•	_		_				_			_	_,	_
	Leu	Val	His		Phe	Arg	Val	Gly		Arg	GIŸ	СТĀ	Pro		Pro
1	•	•	•	5	D	-	•	701- -	10	mh an	Db -	0	*1-	15	N
СТĀ	Arg	Leu		Pro	Pro	Leu	Arg		GIN	Thr	Pne	Ser		vaı	ALÇ
~	C		20	~	3	C	C	25	T	T	N	210	30	270	114.
TÄL	ser	35	GTĀ	TYL	Arg	Ser	40	ser	Leu	Leu	Arg	45	var	WTG	TTE
T 011	7~~		Cln	Lon	Ш-т	۸ ۱۵		Ton	Dro	Arg	7.7.0		Len	λla	Dro
Lieu	50	361	GIII	шец	TTP	55	III	Ter	FIO	ALG	60	FLO	Dea	Aια	110
N~~		Sor	Pro	Sor	λls		Cva	עריים	Va)	Gly		λla	Len	T.e.r	Gls
65	rrp	Ser	FIO	Ser	70	115	Cys	TTP	Val	75	GLY	ıπα	Licu	Dea	80
	Met	Va1	T.en	Ser		Hig	Pro	Hia	T.e.ii	Cys	T.e.ii	Val	Δla	T.e.11	
			204	85	-1-	•••			90	0 12	204			95	-7-
Glu	Ala	Glu	Glu		Pro	Pro	Ala	Ser		Thr	Pro	His	Val		Gly
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Ser	Ara	Phe		Tro	Lvs	Leu	Phe		Gln	Phe	I e u	His		His	Lev
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Leu	Val		Glv	Val	Ala	Val		Leu	Ala	Leu	Glv		Ala	Leu	Val
	130		1			135					140				
Agn		Gln	Ile	Pro	Len		Leu	Glv	G]n	Leu		G] u	Val	Val	Ala
145					150			1		155					160

Lys	Tyr	Thr	Arg	qzA	His	Val	Gly	Ser	Phe	Met	Thr	Glu	Ser	Gln	Asn
				165					170					175	
Leu	Ser	Thr	His	Leu	Leu	Ile	Leu	Tyr	Gly	Val	Gln	Gly	Leu	Leu	Thr
			180					185					190		
Phe	Gly	Tyr	Leu	Val	Leu	Leu	Ser	His	Val	Gly	Glu	Arg	Met	Ala	Val
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Asp	Met	Arg	Arg	Ala	Leu	Phe	Ser	Ser	Leu	Leu	Arg	Tyr	Сув	Gln	Pro
	210					215					220				
Gln	Gly	Ala	Glu	Leu	Gly	Gln	Asp	Ile	Thr	Phe	Phe	Asp	Ala	Asn	Lys
225					230					235					240
Thr	Gly	Gln	Leu	Val	Ser	Arg	Leu	Thr	Thr	Asp	Val	Gln	Glu	Phe	Lys
				245					250					255	
Ser	Ser	Phe	Lys	Leu	Val	Ile	Ser	Gln	Gly	Leu	Arg	Ser	Cys	Thr	Gln
			260					265					270		
Val	Ala	Gly	Суз	Leu	Val	Ser	Leu	Ser	Met	Leu	Ser	Thr	Arg	Leu	Thr
		275					280					285			
Leu	Leu	Leu	Met	Val	Ala	Thr	Pro	Ala	Leu	Met	Gly	Val	Gly	Thr	Leu
	290					295					300				
Met	Gly	Ser	Gly	Leu	Arg	Lys	Leu	Ser	Суз	Gln	Сув	Gln	Glu	Gln	Ile
305					310					315					320
Ala	Arg	Ala	Met	Gly	Val	Ala	Asp	Glu	Ala	Leu	Gly	Asn	Val	Arg	Thr
				325					330					335	
Val	Arg	Ala	Phe	Ala	Met	Glu	Gln	Arg	Glu	Glu	Glu	Arg	Tyr	Gly	Ala
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Glu	Leu	Glu	Ala	Cys	Arg	Cys	Arg	Ala	Glu	Glu	Leu	Gly	Arg	Gly	Ile
		355					360					365			
Ala	Leu	Phe	Gln	Gly	Leu	Ser	Asn	Ile	Ala	Phe	Asn	Сув	Met	Val	Leu
	370					375					380				
Gly	Thr	Leu	Phe	Ile	Gly	Gly	Ser	Leu	Val	Ala	Gly	Gln	Gln	Leu	Thr
385					390					395					400
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Leu

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35 40 45
Ala Ile Val Cys Phe Ala Arg Ser Tyr Asp Gly Asp Phe Val Phe Asp
50 55 60
Asp Ser Glu Ala Ile Val Asn Asn Lys Val Ala Gly Val Val Gly Arg
65 70 75 80
Ala Asp Leu Leu Cys Ala Leu Phe Phe Leu Leu Ser Phe Leu Gly Tyr
85 90 95
Cys Lys Ala Phe Arg Glu Ser Asn Lys Glu Gly Ala His Ser Ser Thr
100 105 110
Phe Trp Val Leu Leu Ser Ile Phe Leu Gly Ala Val Ala Met Leu Cys
115 120 125
Lys Glu Gln Gly Ile Thr Val Leu Gly Leu Asn Ala Val Phe Asp Ile
130 135 140
Leu Val Ile Gly Lys Phe Asn Val Leu Glu Ile Val Gln Lys Val Leu
145 150 155 160
His Lys Asp Lys Ser Leu Glu Asn Leu Gly Met Leu Arg Asn Gly Gly
165 170 175
Leu Leu Phe Arg Met Thr Leu Leu Thr Ser Gly Gly Ala Gly Met Leu
180 185 190
Tyr Val Arg Trp Arg Ile Met Gly Thr Gly Pro Pro Ala Phe Thr Glu
195 200 205
/al Asp Asn Pro Ala Ser Phe Ala Asp Ser Met Leu Val Arg Ala Val
210 215 220
Asn Tyr Asn Tyr Tyr Tyr Ser Leu Asn Ala Trp Leu Leu Leu Cys Pro
225 230 235 240
Trp Trp Leu Cys Phe Asp Trp Ser Met Gly Cys Ile Pro Leu Ile Lys

				245					250					255	
Ser	Ile	Ser	Asp	Trp	Arg	Val	Ile	Ala	Leu	Ala	Ala	Leu	Trp	Phe	Сув
			260					265					270		
Leu	Ile	Gly	Leu	Ile	Cys	Gln	Ala	Leu	Cys	Ser	Glu	Asp	Gly	His	Lya
		275					280					285			
Arg	Arg	Ile	Leu	Thr	Leu	Gly	Leu	Gly	Phe	Leu	Val	Ile	Pro	Phe	Leu
	290					295					300				
Pro	Ala	Ser	Asn	Leu	Phe	Phe	Arg	Val	Gly	Phe	Val	Val	Ala	Glu	Arg
305					310					315					320
Val	Leu	Tyr	Leu	Pro	Ser	Ile	Gly	Tyr	Суз	Val	Leu	Leu	Thr	Phe	Gly
				325					330					335	
Phe	Gly	Ala	Leu	Ser	Lys	His	Thr	Lys	Lys	Lys	Lys	Leu	Ile	Ala	Ala
			340					345					350		
Val	Val	Leu	Gly	Ile	Leu	Phe	Ile	Asn	Thr	Leu	Arg	Cys	Val	Leu	Arg
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Ser	Gly	Glu	Trp	Arg	Ser	Glu	Glu	Gln	Leu	Phe	Arg	Ser	Ala	Leu	Ser
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Val	Сув	Pro	Leu	Asn	Ala	Lys	Val	His	Tyr	Asn	Ile	Gly	Lys	Asn	Leu
385					390					395					400
Ala	Ąsp	Lys	Gly	Asn	Gln	Thr	Ala	Ala	Ile	Arg	Tyr	Tyr	Arg	Glu	Ala
				405					410					415	
Val	Arg	Leu	Asn	Pro	Lys	Tyr	Val	His	Ala	Met	neA	Asn	Leu	Gly	Asn
			420					425					430		
Ile	Leu	Lys	Glu	Arg	Asn	Glu	Leu	Gln	Glu	Ala	Glu	Glu	Leu	Leu	Ser
		435					440					445			
Leu		Val	Gln	Ile	Gln	Pro	Asp	Phe	Ala	Ala	Ala	Trp	Met	Asn	Leu
	450					455					460				
_	Ile	Val	Gln	Asn	Ser	Leu	Lys	Arg	Phe	Glu	Ala	Ala	Glu	Gln	
465					470					475	•				480
Tyr	Arg	Thr	Ala		Lys	His	Arg	Arg	_	Tyr	Pro	Asp	Cys	_	Tyr
				485					490					495	
Asn	Leu	Gly		Leu	Tyr	Ala	qeA		Asn	Arg	His	Val		Ala	Leu
			500					505					510		
Asn	Ala		Arg	Asn	Ala	Thr		Leu	Lys	Pro	Glu		Ser	Leu	Ala
		515					520					525			

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Trp Asn	Asn Me	t Ile	Ile	Leu	Leu	Asp	Asn	Thr	Gly	Asn	Leu	Ala	Gln
530				535					540				
Ala Glu	Ala Va	l Gly	Arg	Glu	Ala	Leu	Glu	Leu	Ile	Pro	Asn	Asp	His
545			550					555					560
Ser Leu	Met Ph	e Ser	Leu	Ala	Asn	Val	Leu	Gly	Lys	Ser	Gln	Lys	Tyr
		565					570				•	575	
Lys Glu	Ser Gl	u Ala	Leu	Phe	Leu	Lys	Ala	Ile	Lys	Ala	Asn	Pro	Asn
	58	0				585					590		
Ala Ala	Ser Ty	r His	Gly	Asn	Leu	Ala	Val	Leu	Tyr	His	Arg	Trp	Gly
	595				600					605			
His Leu	Asp Le	ı Ala	Lys	Lys	His	Tyr	Glu	Ile	Ser	Leu	Gln	Leu	Asp
610	-		-	615		-			620				_
Pro Thr	Ala Se	c Gly	Thr	Lys	Glu	Asn	Tyr	Gly	Leu	Leu	Arg	Arg	Lys
625		-	630	•			•	635			•		640
Leu Glu	Leu Me	t Gln		Lvs	Ala	Val							
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Val	Val	Lys	Glu	Leu	Pro	Glu	Gly	Trp	Ser	Leu	Pro	Ser	Tyr	Val	Ser
		•	20					25					30		
Val	Leu	Val	Ala	Leu	Gly	Asn	Leu	Gly	Leu	Leu	Val	Val	Thr	Leu	Trp
		35					40					45			
Arg	Arg	Leu	Ala	Pro	Gly	Lys	Asp	Glu	Gln	Val	Pro	Ile	Arg	Val	Val
	50					55					60				
Gln	Val	Leu	Gly	Met	Val	Gly	Thr	Ala	Leu	Leu	Ala	Ser	Leu	Trp	His
65					70					75					80
His	Val	Ala	Pro	Val	Ala	Gly	Gln	Leu	His	Ser	Val	Ala	Phe	Leu	Ala
				85					90					95	
Leu	Ala	Phe	Val	Leu	Ala	Leu	Ala	Cys	CAa	Ala	Ser	Asn	Val	Thr	Phe
			100					105					110		
Leu	Pro		Leu	Ser	His	Leu		Pro	Arg	Phe	Leu		Ser	Phe	Phe
		115					120					125			
Leu		Gln	Gly	Leu	Ser		Leu	Leu	Pro	Cys		Leu	Ala	Leu	Val
	130				_	135	÷			_	140				
	Gly	Val	Gly	Arg		Glu	Суз	Pro	Pro		Pro	Ile	Asn	Gly	
145		_	_	_	150		_		_	155 	_		_		160
Pro	GIĀ	Pro	Pro		qeA	Pne	Leu	GIU	-	Phe	Pro	Ala	Ser		Phe
5 1-		• • -	•	165	••-	•	•	••••	170					175	- 2-
Pne	тър	ATA	Leu	TIT	ALA	Leu	rea		ATA	ser	ALA	ATG		Pne	GIN
~ 3	T	T	180	T	•	D	D	185	5	0	*** 1	D	190	0]	6 3
стХ	теп		Leu	Leu	Leu	LIO		KLO	r.o	ser	var		TUL	чтλ	GIU
T	61	195	01- -	T	41	****1	200	.1.		0 1	••	205	~ 3	a 1	··- 1
Leu	_	ser	Gly	reg	GTU		отА	WTG	\$10	αтλ		GTI	GTI	GTA	AST
C1	210	°	Se	Dva	Ton	215	61 14	D	7)	C	220	31 -	73 -	C1	mh
G1u 225	GIU	aer.	Ser	PLO		GTII	GIU	PLO			GIN	ATG .	ътg	стХ	
44 3					230					235					240

Thr	Pro	Gly	Pro	Asp	Pro	Lys	Ala	Tyr	Gln	Leu	Leu	Ser	Ala	Arg	Ser
				245					250					255	
Ala	Cys	Leu	Leu	Gly	Leu	Leu	Ala	Ala	Thr	Asn	Ala	Leu	Thr	Asn	Gly
			260					265					270		
Val	Leu	Pro	Ala	Val	Gln	Ser	Phe	Ser	Суз	Leu	Pro	Tyr	Gly	Arg	Leu
		275					280					285			
Ala	Tyr	His	Leu	Ala	Val	Val	Leu	Gly	Ser	Ala	Ala	Asn	Pro	Leu	Ala
	290					295					300				
Cys	Phe	Leu	Ala	Met	Gly	Val	Leu	Суз	Arg	Ser	Leu	Ala	Gly	Leu	Gly
305					310					315					320
Gly	Leu	Ser	Leu	Leu	Gly	Val	Phe	Cys	Gly	Gly	Tyr	Leu	Met	Ala	Leu
				325					330					335	
Ala	Val	Leu	Ser	Pro	Cys	Pro	Pro	Leu	Val	Gly	Thr	Ser	Ala	Gly	Val
			340					345					350		
Val	Leu	Val	Val	Leu	Ser	Trp	Val	Leu	Сув	Leu	Gly	Val	Phe	Ser	Tyr
		355					360					365			
Val	Lys	Val	Ala	Ala	Ser	Ser	Leu	Leu	His	Gly	Gly	Gly	Arg	Pro	Ala
	370					375					380				
Leu	Leu	Ala	Ala	Gly	Val	Ala	Ile	Gln	Val	Gly	Ser	Leu	Leu	Gly	Ala
385					390					395					400
Val	Ala	Met	Phe	Pro	Pro	Thr	Ser	Ile	Tyr	His	Val	Phe	His	Ser	Arg
				405					410					415	
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Val Tyr Ala Leu Val Val Val Ser Tyr Phe Leu Ile Thr Gly Gly Il

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Glu	His	Gly	His	Gln	Arg	Pro	Val	Ala	Phe	Leu	Ala	Tyr	Arg	Val	Ası
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Gly	Gln	Tyr	Ile	Met	Glu	Gly	Leu	Ala	Ser	Ser	Phe	Leu	Phe	Thr	Met
				85					90					95	
Gly	Gly	Leu	_	Phe	Ile	Ile	Leu	qeA	Arg	Ser	Asn	Ala		Asn	Ile
			100					105		_			110		_
Pro	Lys		Asn	Arg	Phe	Leu		Leu	Phe	Ile	Gly		Val	Суз	Va]
_	_	115	_,	_,			120	•	_,			125			
Leu		Ser	Phe	Phe	Met		Arg	Val	Phe	Met	-	Met	гуs	Leu	Pro
0 3	130	T	> 0-4-	a 1		135					140				
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Lys	Arg	Lys	Ser	Ser	Leu	Leu	Leu	Lys	Leu	Ile	Ala	Val	Val	Phe	Ala
			20					25					30		
Val	Leu	Leu	Phe	Cys	Glu	Phe	Leu	Ile	Tyr	Tyr	Leu	Ala	Ile	Phe	Gln
		35					40					45			
Cys		Trp	Pro	Glu	Val	_	Thr	Thr	Ala	Ser	-	Gly	Glu	Gln	Thr
	50			_		55	_				60		_		_
	Arg	Glu	Pro	Val		Lys	Ala	Met	Phe		Ala	Asp	Thr	His	
65 -				_	70	•	_	_		75 -	_	_	_		_ 80 _
Leu	GIA	GIU	Phe		GŢĀ	Hls	Trp	Leu	_	гЛа	Leu	Arg	Arg		Trp
~ 1-	16 -+	~ 1	3	85	mt -	01	mb	3 1 -	90		T	7	~ 1	95	~ 1
GIN	Jen	GIU	Arg	ATØ	rne	GTU	TIL	Ala	ьеи	TIP	Leu	neu	GIN 110	LIO	GIU

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Val	Val	Phe	Ile	Leu	Gly	Asp	Ile	Phe	Asp	Glu	Gly	rys	Trp	Ser	Th
		115					120					125			
Pro	Glu	Ala	Trp	Ala	Asp	Asp	Val	Glu	Arg	Phe	Gln	Lys	Met	Phe	Ar
	130					135					140				
His	Pro	Ser	His	Val	Gln	Leu	Lys	Val	Val	Ala	Gly	Asn	His	Asp	Ile
145					150					155					160
Gly	Phe	His	Tyr	Glu	Met	Asn	Thr	Tyr	Lys	Val	Glu	Arg	Phe	Glu	Lys
				165					170					175	
Val	Phe	Ser	Ser	Glu	Arg	Leu	Phe	Ser	Trp	Lys	Gly	Ile	Asn	Phe	Va]
			180					185	•				190		
Met	Val	Asn	Ser	Val	Ala	Leu	Asn	Gly	Asp	Gly	Cys	Gly	Ile	Cys	Sei
		195					200					205			
Glu	Thr	Glu	Ala	Glu	Leu	Ile	Glu	Val	Ser	His	Arg	Leu	Asn	Суз	Ser
	210					215					220				
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120/233

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360

420 480

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Thr	Pro	Gly	Pro	Asp	Pro	Lys	Ala	Tyr	Gln	Leu	Leu	Ser	Ala	Arg	Ser	
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Ala	Сув	Leu	Leu	Gly	Leu	Leu	Ala	Ala	Thr	Asn	Ala	Leu	Thr	neA	Gly	
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Val	Leu	Pro	Ala	Val	Gln	Ser	Phe	Ser	Сув	Leu	Pro	Tyr	Gly	Arg	Leu	
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Ala	Tyr	His	Leu	Ala	Val	Val	Leu	Gly	Ser	Ala	Ala	Asn	Pro	Leu	Ala	
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Cya	Phe	Leu	Ala	Met	Gly	Val	Leu	Cys	Arg	Ser	Leu	Ala	Gly	Leu	Gly	
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ggc	ctc	tct	ctg	ctg	ggc	gtg	ttc	tgt	ggg	ggc	tac	ctg	atg	gcg	ctg	1187
Gly	Leu	Ser	Leu	Leu	Gly	Val	Phe	Cys	Gly	Gly	Tyr	Leu	Met	Ala	Leu	
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Ala	Val	Leu	Ser	Pro	Cys	Pro	Pro	Leu	Val	Gly	Thr	Ser	Ala	Gly	Val	•
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Val	Leu	Val	Val	Leu	Ser	Trp	Val	Leu	Сув	Leu	Gly	Val	Phe	Ser	Tyr	
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Val	Lys	Val	Ala	Ala	Ser	Ser	Leu	Leu	His	Gly	Gly	Gly	Arg	Pro	Ala	
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Leu	Leu	Ala	Ala	Gly	Val	Ala	Ile	Gln	Val	Gly	Ser	Leu	Leu	Gly	Ala	
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Val	Ala	Met	Phe	Pro	Pro	Thr	Ser	Ile	Tyr	His	Val	Phe	His	Ser	Arg	
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aag	gac	tgt	gca	gac	ccc	tgt	gac	tcc	tgag	ectg	igg c	aggt	gggg	a co	ecege	1480
Lys	Asp	Суз	Ala	Ąsp	Pro	Суз	Asp	Ser								
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Lys Leu Lys Lys Pro Pro Trp Leu His Met Pro Ser Ala Met Thr Val													
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Leu Ser Phe Phe Met Ala Arg Val Phe Met Arg Met Lys Leu Pro Gly	
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Tyr_Leu Met Gly	
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Met Ala Met Ile	
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Ser	Leu	Leu	Leu	Lys	Leu	Ile	Ala	Val	Val	Phe	Ala	Val	Leu	Leu	Phe	
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Cys	Glu	Phe	Leu	Ile	Tyr	Tyr	Leu	Ala	Ile	Phe	Gln	Суз	Asn	Trp	Pro	
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3lu	Arg	Leu	Phe	Ser	Trp	Lys	Gly	Ile	Asn	Phe	Val	Met	Val	Asn	Ser	•
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Glu	Leu	Ile	Glu	Val	Ser	His	Arg	Leu	Asn	Суз	Ser	Arg	Glu	Ala	Arg	
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Gly	Ser	Ser	Arg	Cys	Gly	Pro	Gly	Pro	Leu	Leu	Pro	Thr	Ser	Ala	Pro	
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Val	Leu	Leu	Gln	His	Tyr	Pro	Leu	Tyr	Arg	Arg	Ser	Asp	Ala	Asn	Суз	
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Ser	Gly	Glu	Asp	Ala	Ala	Pro	Ala	Glu	Glu	Arg	Asp	Ile	Pro	Phe	Lys	
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Glu	Asn	Tyr	Asp	Val	Leu	Ser	Arg	Glu	Ala	Ser	Gln	Lys	Leu	Leu	Trp	
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tgg	ctc	cag	ccg	cgc	ctg	gtt	ctc	agt	ggc	cac	acg	cac	agc	gcc	tgc	1145
Trp	Leu	Gln	Pro	Arg	Leu	Val	Leu	Ser	Gly	His	Thr	His	Ser	Ala	Суз	
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_			His			-	-				_	_				
	310			_	_	315					320					
agt	tgg	agg	aac	aga	aac	aac	ccc	agt	ttc	atc	atg	ggt	agc	atc	acg	1241
			Asn	-				_			_	-				
325		-		-	330					335		_			340	
ccc	aca	gac	tac	acc	ctc	tcc	aaq	tge	tac	ctc	cca	cgt	gag	gat	gtg	1289
			Tyr				-	-								
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			Ile													
			360		4	2		365	2				370			
ctc	act	cac	ttt	aaa	ctt	cta	acc		act.	ttt	ctt	tct		tta	aac	1385
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Met Ile Arg Gln Glu Arg Ser Thr Ser Tyr Gln Glu Leu	
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Ser Glu Glu Leu Val Gln Val Val Glu Asn Ser Glu Leu Ala Asp Glu	
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Gln Asp Lys Glu Thr Val Arg Val Gln Gly Pro Gly Ile Leu Pro Gly	
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Leu Lys Asn Val Phe Ser Val Leu Leu Ile Phe Ile Tyr Leu Leu Leu	
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Met Ala Val Ala Val Phe Leu Val Tyr Arg Thr Ile Thr Asp Phe Arg	
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Arg	Tyr	Asp	Ala	Pro	Gly	Ile	Ala	Leu	Tyr	Pro	Gly	Gln	Ala	Gln	Leu	
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Leu	Ser	Суз	Lys	His	His	Tyr	Glu	Val	Ile	Pro	Pro	Leu	Thr	Ser	Pro	
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Gly	Gln	Pro	Gly	Asp	Met	Asn	Суз	Thr	Thr	Gln	Arg	Ile	Asn	Tyr	Thr	
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Asp	Pro	Phe	Ser	Asn	Gln	Thr	Val	Lys	Ser	Ala	Leu	Ile	Val	Gln	Gly	
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Pro	Arg	Glu	Val	Lys	Lys	Arg	Glu	Leu	Val	Phe	Leu	Gln	Phe	Arg	Leu	
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cacg atg	g act	t at	ca	e ato	e et	c at	c ct	g ct	g tt	g ct	e et	c gc	c tt	C	286
Met	: Th	r Ile	e Hi:	s Ile	e Le	u Il	e Le	u Le	u Le	u Le	u Le	u Al	a Ph	9	
1	ļ			!	5				1	0					
tcc gcc	caa	ggg	gac	ctg	gac	act	gca	gcc	agg	cga	ggc	cag	cac	cag	. 334
Ser Ala	Gln	Gly	Asp	Leu	Asp	Thr	Ala	Ala	Arg	Arg	Gly	Gln	His	Gln	
15				20					25					30	
gte ece	_		-			-	_		_		-	_			382
Val Pro	Gln	His	_	Gly	His	Val	Cys	_	Leu	Gly	Val	Cys		Thr	
			35					40					45		4
cac cgc	_	•							-	_					430
His Arg	Leu		GIU	TTE	TTG	туг		He	Arg	Cys	Leu		GIN	GIÀ	·
	~~~	50	<i>aa</i> a	<b>~~</b>			55				a+ n	60	ata	+ aa	478
gcc ctc Ala Leu		•		-		-	-					_			4/0
AIG Leu	65 65	GIU	GIY	GIII	FIO	70	ALG	PLO	GLY	FIO	75	GLII	Tiou	115	
geg eeg		ata	aca	cga	aac		age	cca	σct	caa		cca	gga	ttc	526
Ala Pro			-			_		_	-				_	_	
80					85					90			•		
egg cet	gca	geg	agg	ggg	cta	geg	cag	tgc	cca	gct	ege	tgg	gtg	acc	574
Arg Pro	Ala	Ala	Arg	Gly	Leu	Ala	Gln	Cys	Pro	Ala	Arg	Trp	Val	Thr	
95				100					105			•		110	
teg gge	acg	gct	cgt	ccc	ctc	ctc	ggc	ttc	agt	ttg	cct	atc	tgt	atg	622
Ser Gly	Thr	Ala	Arg	Pro	Leu	Leu	Gly	Phe	Ser	Leu	Pro	Ile	Суз	Met	
			115					120					125		
ttg gag	ctt	cta	ctc	cac	att	tct	tct	ccc	cta	act	cca	gcc	cct	gaa	670
Leu Glu	Leu	Leu	Leu	His	Ile	Ser	Ser	Pro	Leu	Thr	Pro	Ala	Pro	Glu	
		130					135					140			
acc gtc	ttc	ccc	agt	ccc	tcc	ccg	ggc	tge	gac	tagg	rttgg	jac d	etaga	ag	720
Thr Val	Phe	Pro	Ser	Pro	Ser	Pro	Gly	Суз	qzA						

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gtg			783
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Pro Gly Leu Glu Ala	Val Pro Pro Val	Ala Pro Pro Pro Al	a Thr Ala
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Ala Ser Gly Pro Ile	Pro Lys Ser Gly	Pro Glu Pro Lys Ar	g Arg His
35	40	45	
Leu Gly Thr Leu Leu	Gln Pro Thr Val	Asn Lys Phe Ser Le	u Arg Val
50	55	60	•
Phe Gly Ser His Lys	Ala Val Glu Ile	Glu Gln Glu Arg Va	l Lys Ser
65	70	<b>75</b>	80
Ala Gly Ala Trp Ile	Ile His Pro Tyr	Ser Asp Phe Arg Ph	e Tyr Trp
85		90	95
Asp Leu Ile Met Leu	Leu Leu Met Val	Gly Asn Leu Ile Va	l Leu Pro
100	105	11	0
Val Gly Ile Thr Phe	Phe Lys Glu Glu	Asn Ser Pro Pro Tr	p Ile Val
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Phe Asn Val Leu Ser	Asp Thr Phe Phe	Leu Leu Asp Leu Va	l Leu Asn
130	135	140	
Phe Arg Thr Gly Ile	Val Val Glu Glu	Gly Ala Glu Ile Le	
145	150	155	160
Pro Arg Ala Ile Arg	Thr Arg Tyr Leu	Arg Thr Trp Phe Le	ı Val Asp
165		170	175
Leu Ile Ser Ser Ile	Pro Val Asp Tyr		
180	185	19	)
Glu Pro Arg Leu Asp	Ala Glu Val Tyr	Lys Thr Ala Arg Ala	a Leu Arg
195	200	. 205	·
•			

Ile	Val	Arg	Phe	Thr	Lys	Ile	Leu	Ser	Leu	Leu	Arg	Leu	Leu	Arg	Lev
	210					215					220				
Ser	Arg	Leu	Ile	Arg	Tyr	Ile	His	Gln	Trp	Glu	Glu	Ile	Phe	His	Met
225					230					235					240
Thr	Tyr	Asp	Leu	Ala	Ser	Ala	Val	Val	Arg	Ile	Phe	Asn	Leu	Ile	Gly
				245					250					255	
Met	Met	Leu	Leu	Leu	Суз	His	Trp	Asp	Gly	Суз	Leu	Gln	Phe	Leu	Val
			260					265					270		
Pro	Met	Leu	Gln	Asp	Phe	Pro	Pro	Asp	Сув	Trp	Val	Ser	Ile	Asn	His
		275					280					285			
Met	Val	Val	Arg	Ser	Pro	His	Ser	Ser	Ala	Phe	Pro	Gly	Pro	Ser	
	290					295					300				
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	1> 28														
	2> PI														
			sapie	ens											
	0> 92						_								
	Ala	Asp	Pro		Gln	Leu	Phe	Asp		Thr	Ser	Ser	Ala		Ser
1				5					10	_		_		15	
Arg	Gly	Tyr	-	Ala	Gln	Arg	Ala		Gly	Gly	Leu	Ser		Pro	Ala
			20					25					30		_
Ala	Ser		Thr	Pro	His	Ala		Phe	Leu	Ala	Asp		Val	Ser	Asn
		35		_		_	40	_				45	•	-1	<b>-</b>
Met		Met	Ala	Tyr	GIY		Ser	Leu	Ala	Ala		GIĀ	гÀз	GIU	ren
•• - <b>•</b>	50	•	•			55	mh -	<b>-1</b> .		-1-	60	T	7	T	<b></b>
	Asp	гла	Asn	TTE	_	Arg	Pne	TTE	Pro	Ile	Thr	гуа	Leu	гла	
65 —	nh.	21-	**-3	3	70	\/_ <del>-</del>	m	*** 1	<b>41</b>	75	T	T	C1	T 011	80
TYE	Pne	ATG	val		Thr	Met	туг	vaı	_	Arg	гув	Leu	GŢĀ		Ten
<b>D</b> L -	Dh.	<b>D</b>	<b>.</b>	85		<b>0</b> 3	•	<b></b>	90		<b>63</b>	<b></b>	01-	95	3
Pne	Pne	PLO	_	ren	HIS	GIN	Asp		GIU	Val	GIN	туг		GIN	Asp
<b></b> 1	<b>5</b> -	••-	100	D.	•	<b>-1</b>	•	105			<b>-</b>	<b>3</b>	110	<b>m</b>	<b>-</b> 7 -
TNT	PTO		ALA	Pro	Arg	Phe	_	vaı	Asn	Ala	PTO	_	ьeu	т <b>ў</b> г	тте
	.,	115		<b>-1</b> .	_,	_,	120	••-	<b>-</b> .	17a l		125	T	<b>\1</b> =	
DTC-	AIA	MAT	AIA	PU6	116	יייחיוי	יייייי	VAI	1.011	VAI	AIA	C+IV		AIR	ווביו

	130					135					140				
Gly	Thr	Gln	Asp	Arg	Phe	Ser	Pro	Asp	Leu	Leu	Gly	Leu	Gln	Ala	Ser
145					150					155					160
Ser	Ala	Leu	Ala	Trp	Leu	Thr	Leu	Glu	Val	Leu	Ala	Ile	Leu	Leu	Ser
				165					170					175	
Leu	Tyr	Leu	Val	Thr	Val	Asn	Thr	Asp	Leu	Thr	Thr	Ile	Asp	Leu	Val
			180					185					190		
Ala	Phe	Leu	Gly	Tyr	Lys	Tyr	Val	Gly	Met	Ile	Gly	Gly	Val	Leu	Met
		195					200					205			
Gly	Leu	Leu	Phe	Gly	Lys	Ile	Gly	Tyr	Tyr	Leu	Val	Leu	Gly	Trp	Суз
	210					215					220				
Сув	Val	Ala	Ile	Phe	Val	Phe	Met	Ile	Arg	Thr	Leu	Arg	Leu	Lys	Ile
225					230					235					240
Leu	Ala	Asp	Ala	Ala	Ala	Glu	Gly	Val	Pro	Val	Arg	Gly	Ala	Arg	Asn
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Gln	Leu	Arg		Tyr	Leu	Thr	Met	Ala	Val	Ala	Ala	Ala		Pro	Met
			260					265					270		
Leu	Met	_	Trp	Leu	Thr	Phe		Leu	Val	Arg					
		275					280								
-01	· ·														
	0> 93														
	1> 48														
	2> PF														
	3> Ho 0> 93		sabre	aus			•								
	Ala		T 170	G1v	Sor	e	C1v	2~~	2~~	Dwo	Tou	Tou	T 611	G) v	T.e.ii
Mec 1	Ala	GTÅ	пåя	<b>G1</b> 9	ser	ser	GTĀ	ALG	10	PIO	Ten	neu	Dea	15	Deu
	Val	A 1 m	17a1		mh~	1701	ui o	T 011	_	TIO	Ciro	Dro	Пчт		Twa
Dea	٧	ALG	20	Ala	1111	vai	ura	25	val	116	СуБ	FLO	30	1111	Lys
Val	Glu	Glu		Dhe	Δen	T. <b>2</b> 11	Gln		Thr	uie	) an	T.e.11		ጥህጕ	His
•	<b></b>	35	501	FIIC	וופת	Den	40	ALG	1111	птэ	DP	45	Ten	-1-	1140
כדינים	Gln		T.e.n	Glu	Gln	ጥነກ		uie	T.e.n	GIn	Dhe		Glv	Val	Val
5	50	_			~_11	55			ar-cu	JIU	60		1		
Pro	Arg		Phe	Leu	Glv		Val	Val	Ile	Ala		Phe	Ser	Ser	Pro
65					70					75					80

Ala	Val	Tyr	Val	Leu	Ser	Leu	Leu	Glu	Met	Ser	Lys	Phe	Tyr	Ser	Glr
				85					90					95	
Leu	Ile	Val	Arg	Gly	Val	Leu	Gly	Leu	Gly	Val	Ile	Phe	Gly	Leu	Tr
			100					105					110		
Thr	Leu	Gln	Lys	Glu	Val	Arg	Arg	His	Phe	Gly	Ala	Met	Val	Ala	Thr
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Met	Phe	Суз	Trp	Val	Thr	Ala	Met	Gln	Phe	His	Leu	Met	Phe	Tyr	Cys
	130					135					140				
Thr	Arg	Thr	Leu	Pro	Asn	Val	Leu	Ala	Leu	Pro	Val	Val	Leu	Leu	Ala
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Leu	Ala	Ala	Trp	Leu	Arg	His	Glu	Trp	Ala	Arg	Phe	Ile	Trp	Leu	Ser
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Ala	Phe	Ala	Ile	Ile	Val	Phe	Arg	Val	Glu	Leu	Суз	Leu	Phe	Leu	Gly
			180					185					190		
Leu	Leu	Leu	Leu	Leu	Ala	Leu	Gly	Asn	Arg	Lys	Val	Ser	Val	Val	Arg
		195					200					205			
Ala	Leu	Arg	His	Ala	Val	Pro	Ala	Gly	Ile	Leu	Cya	Leu	Gly	Leu	Thr
	210					215					220				
Val	Ala	Val	Asp	Ser	Tyr	Phe	Trp	Arg	Gln	Leu	Thr	Trp	Pro	Glu	Gly
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Lys	Val	Leu	Trp	Tyr	Asn	Thr	Val	Leu	Asn	Lys	Ser	Ser	Asn	Trp	Gly
				245					250					255	
Thr	Ser	Pro	Leu	Leu	Trp	Tyr	Phe	Tyr	Ser	Ala	Leu	Pro	Arg	Gly	Leu
			260					265					270		
Gly	Суз	Ser	Leu	Leu	Phe	Ile	Pro	Leu	Gly	Leu	Val	Asp	Arg	Arg	Thr
		275					280					285			
His	Ala	Pro	Thr	Val	Leu	Ala	Leu	Gly	Phe	Met	Ala	Leu	Tyr	Ser	Leu
	290					295					300				
Leu	Pro	His	Lys	Glu	Leu	Arg	Phe	Ile	Ile	Tyr	Ala	Phe	Pro	Met	Leu
305					310					315					320
Asn	Ile	Thr	Ala	Ala	Arg	Gly	Cys	Ser	Tyr	Leu	Leu	Asn	Asn	Tyr	Lys
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Lys	Ser	Trp	Leu	Tyr	Lys	Ala	Gly	Ser	Leu	Leu	Val	Ile	Gly	His	Leu
			340					345					350		
Val	Val	Asn	Ala	AΙA	ጥህን፦	Ser	Ala	Thr	Ala	Leu	TVY	Val.	Ser	His	Phe

		355					360					365			
Asn	Tyr	Pro	Gly	Gly	Val	Ala	Met	Gln	Arg	Leu	His	Gln	Leu	Val	Pro
	370					375					380				
Pro	Gln	Thr	Asp	Val	Leu	Leu	His	Ile	Asp	Val	Ala	Ala	Ala	Gln	Thr
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Gly	Val	Ser	Arg	Phe	Leu	Gln	Val	Asn	Ser	Ala	Trp	Arg	Tyr	Asp	Lys
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Arg	Glu	Asp	Val	Gln	Pro	Gly	Thr	Gly	Met	Leu	Ala	Tyr	Thr	His	Ile
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Leu	Met	Glu	Ala	Ala	Pro	Gly	Leu	Leu	Ala	Leu	Tyr	Arg	Asp	Thr	His
		435					440					445			
Arg	Val	Leu	Ala	Ser	Val	Val	Gly	Thr	Thr	Gly	Val	Ser	Leu	Asn	Leu
	450					455					460				
Thr	Gln	Leu	Pro	Pro	Phe	Asn	Val	His	Leu	Gln	Thr	Lys	Leu	Val	Leu
465					470					475					480
Leu	Glu	Arg	Leu	Pro	Arg	Pro	Ser								
				485				•							
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	1> 18														
	2> PI		:												
	3> A0 0> 94		sapie	ans											
			Dro	) an	Pro	Asp.	Pro	Aan	Dro	Nan	Dro	Glu	Pro	Δla	Glv
1	TIP	PIO	PLO	лэр 5	PLO	wab.	PIO	Авр	10	wab	PIO	Gra	FIO	15	GIJ
	Sor	Ara	Bro		Pro	Ala	Val	Dro		Lan	Ara	λla	T.e.11		Pro
GLY	DET	n.y	20	Gıy	FLO	ALU.	var	25	Gry	Den	мy	nia.	30	204	
Ala	Ara	Ala		T.e.u	Cvs	Ser	T.eu		Glv	Þrα	Tell	ĭ.e.ii		Ala	Glu
2224	9	35	1110		CJD	-	40	<b></b>	011	an y		45			
Ser	ឲាប		Ser	Dhe	Tle	Thr		Tle	Cva	ጥህን	Va1		Ser	Ser	Ala
-	50		-		110	55		110	Cyb	-1-	60		-		
Ser		Phe	T.e.11	ጥኮኮ	Ala	Pro	T.em	T.en	Glu	Phe		ī.eu	Ala	Leu	TVI
65					70					75					80
	Leu	Phe	Ala	Asp		Met	Gln	Leu	Asn		Lvs	Trp	Gln	Gly	_
				85					90	F	-4 -	<b>L</b> -		95	

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A														
CAB JI	p Pro	Met	Met	Asp	Phe	Leu	Arg	Cys	Val	Thr	Ala	Ala	Leu	Ile
		100					105		٠			110		
Tyr Ph	e Ala	Ile	Ser	Ile	Thr	Ala	Ile	Ala	Lys	Tyr	Ser	Asp	Gly	Ala
	115					120					125			
Ser Ly	s Ala	Ala	Gly	Val	Phe	Gly	Phe	Phe	Ala	Thr	Ile	Val	Phe	Ala
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Thr As	p Phe	Tyr	Leu	Ile	Phe	Asn	Asp	Val	Ala	Lys	Phe	Leu	Lys	Gln
145				150					155					160
Gly As	p Ser	Ala	Asp	Glu	Thr	Thr	Ala	His	Lys	Thr	Glu	Glu	Glu	Asn
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Ser As	e Ser	qeA	Ser	Asp										
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Met Asj	o Gly		5		_			10					15	
Met Asj	o Gly		5		_			10					15	
Met Asj	o Gly	Glu 20	5 Val	Leu	Gly	Ala	Leu 25	10 Glu	Ala	Lys	Thr	Gly 30	15 Val	Glu
Met Asj 1 Leu Vai	o Gly	Glu 20	5 Val	Leu	Gly	Ala	Leu 25	10 Glu	Ala	Lys	Thr	Gly 30	15 Val	Glu
Met Asj 1 Leu Vai	Gly Thr Tyr 35	Glu 20 Leu	5 Val Ala	Leu Ala	Gly	Ala Ala 40	Leu 25 Val	10 Glu Thr	Ala Leu	Lys Leu	Thr Ser 45	Gly 30 Leu	15 Val Tyr	Glu Leu
Met Asj 1 Leu Vai Lys Arg	Gly Thr Tyr 35 Gly	Glu 20 Leu	5 Val Ala	Leu Ala	Gly	Ala Ala 40	Leu 25 Val	10 Glu Thr	Ala Leu	Lys Leu	Thr Ser 45	Gly 30 Leu	15 Val Tyr	Glu Leu
Met Asj 1 Leu Val Lys Arc	Gly Thr Tyr 35 Gly	Glu 20 Leu Tyr	5 Val Ala Gly	Leu Ala Ala	Gly Gly Ser 55	Ala Ala 40 Leu	Leu 25 Val Leu	10 Glu Thr Cys	Ala Leu Asn	Lys Leu Leu 60	Thr Ser 45 Ile	Gly 30 Leu Gly	15 Val Tyr Phe	Glu Leu Val
Met Asj 1 Leu Vai Lys Arg Leu Pho	Gly Thr Tyr 35 Gly	Glu 20 Leu Tyr	5 Val Ala Gly	Leu Ala Ala	Gly Gly Ser 55	Ala Ala 40 Leu	Leu 25 Val Leu	10 Glu Thr Cys	Ala Leu Asn	Lys Leu Leu 60	Thr Ser 45 Ile	Gly 30 Leu Gly	15 Val Tyr Phe	Glu Leu Val
Met Asj 1 Leu Val Lys Arg Leu Pho 50 Tyr Pro	Gly Thr 35 Gly Ala	Glu 20 Leu Tyr	5 Val Ala Gly Ala	Leu Ala Ala Ser 70	Gly Ser 55	Ala Ala 40 Leu Lys	Leu 25 Val Leu Ala	10 Glu Thr Cys	Ala Leu Asn Glu 75	Lys Leu Leu 60 Ser	Thr Ser 45 Ile Pro	Gly 30 Leu Gly Ser	15 Val Tyr Phe Lys	Glu Leu Val Asp 80
Met Asj 1 Leu Val Lys Arg Leu Pho 50 Tyr Pro 65	Gly Thr 35 Gly Ala	Glu 20 Leu Tyr	5 Val Ala Gly Ala	Leu Ala Ala Ser 70	Gly Ser 55	Ala Ala 40 Leu Lys	Leu 25 Val Leu Ala	10 Glu Thr Cys	Ala Leu Asn Glu 75	Lys Leu Leu 60 Ser	Thr Ser 45 Ile Pro	Gly 30 Leu Gly Ser	15 Val Tyr Phe Lys	Glu Leu Val Asp 80
Met Asj 1 Leu Val Lys Arg Leu Pho 50 Tyr Pro 65	Gly Thr 35 Gly Ala	Glu 20 Leu Tyr Tyr	5 Val Ala Gly Ala Trp 85	Leu Ala Ala Ser 70 Leu	Gly Ser 55 Ile	Ala 40 Leu Lys	Leu 25 Val Leu Ala Trp	10 Glu Thr Cys Ile Val 90	Ala Leu Asn Glu 75 Val	Lys Leu 60 Ser Tyr	Thr Ser 45 Ile Pro	Gly 30 Leu Gly Ser	15 Val Tyr Phe Lys Phe 95	Glu Leu Val Asp 80 Gly
Met Asj 1 Leu Val Lys Arc Leu Pho 50 Tyr Pro 65 Asp Asj	Gly Thr 35 Gly Ala	Glu 20 Leu Tyr Tyr	5 Val Ala Gly Ala Trp 85	Leu Ala Ala Ser 70 Leu	Gly Ser 55 Ile	Ala 40 Leu Lys	Leu 25 Val Leu Ala Trp	10 Glu Thr Cys Ile Val 90	Ala Leu Asn Glu 75 Val	Lys Leu 60 Ser Tyr	Thr Ser 45 Ile Pro	Gly 30 Leu Gly Ser	15 Val Tyr Phe Lys Phe 95	Glu Leu Val Asp 80 Gly
Met Asj 1 Leu Val Lys Arc Leu Pho 50 Tyr Pro 65 Asp Asj	Gly Thr 35 Gly Ala Thr	Glu 20 Leu Tyr Tyr Val Phe 100	5 Val Ala Gly Ala Trp 85	Leu Ala Ala Ser 70 Leu Ser	Gly Ser 55 Ile Thr	Ala 40 Leu Lys Tyr	Leu 25 Val Leu Ala Trp Leu 105	10 Glu Thr Cys Ile Val 90 Leu	Ala Leu Asn Glu 75 Val	Leu Leu 60 Ser Tyr	Thr Ser 45 Ile Pro Ala	Gly 30 Leu Gly Ser Leu Pro 110	15 Val Tyr Phe Lys Phe 95	Glu Leu Val Asp 80 Gly
Met Asj 1 Leu Val Lys Arg Leu Pho 50 Tyr Pro 65 Asp Asj Leu Ala	Gly Thr 35 Gly Ala Thr	Glu 20 Leu Tyr Tyr Val Phe 100	5 Val Ala Gly Ala Trp 85	Leu Ala Ala Ser 70 Leu Ser	Gly Ser 55 Ile Thr	Ala 40 Leu Lys Tyr	Leu 25 Val Leu Ala Trp Leu 105	10 Glu Thr Cys Ile Val 90 Leu	Ala Leu Asn Glu 75 Val	Leu Leu 60 Ser Tyr	Thr Ser 45 Ile Pro Ala	Gly 30 Leu Gly Ser Leu Pro 110	15 Val Tyr Phe Lys Phe 95	Glu Leu Val Asp 80 Gly

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<211> 153

<212> PRT

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			20					25					30		
Leu	His	Ile	Val	Leu	Leu	Ser	Ile	Pro	Phe	Phe	Ser	Val	Pro	Val	Ala
		35					40					45			
Trp	Thr	Leu	Thr	Asn	Ile	Ile	His	Asn	Leu	Gly	Met	Tyr	Val	Phe	Leu
	50					55					60				
His	Ala	Val	Lys	Gly	Thr	Pro	Phe	Glu	Thr	Pro	qeA	Gln	Gly	Lys	Ala
65					70					75					80
Arg	Leu	Leu	Thr	His	Trp	Glu	Gln	Leu	Asp	Tyr	Gly	Val	Gln	Phe	Thr
				85					90					95	
Ser	Ser	Arg	Lys	Phe	Phe	Thr	Ile	Ser	Pro	Ile	Ile	Leu	Tyr	Phe	Leu
			100					105					110		
Ala	Ser	Phe	Tyr	Thr	Lys	Tyr	Asp	Pro	Thr	His	Phe	Ile	Leu	Asn	Thr
		115					120					125			
Ala	Ser	Leu	Leu	Ser	Val	Leu	Ile	Pro	Lys	Met	Pro	Gln	Leu	His	Gly
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Val	Arg	Ile	Phe	Gly	Ile	Asn	Lys	Tyr							
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Gly	Val	Leu	Ala	Gly	Thr	Met	Ala	Thr	Val	Val	Ala	Ile	Thr	Val	Leu
			20					25					30		
Ile	Ser	Thr	Ala	Thr	Phe	Trp	Arg	Asn	Lys	Lys	Ser	Asn	Lys	Val	Leu
		35					40					45			

Pro Met Arg Arg Val Leu Arg Lys Arg Pro Ser Pro Ala Pro Arg Thr

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Cys Val Ala Ile Phe Val Phe Met Ile Arg Thr Leu Arg Leu Lys Ile	
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becomests as the est see that the because one and and atta	288

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ctg	ctg	ggg	ctg	ctg	gtg	gcc	gta	gcc	act	gtc	cac	ctg	gto	atc	tgt		336
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Phe	Ser	Ser	Pro	Ala	Val	Tyr	Val		Ser	Leu	Leu	Glu		Ser	Lys		
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Ile	Gly	His	Leu	Val	Val	Asn	Ala	Ala	Tyr	Ser	Ala	Thr	Ala	Leu	Tyr	
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Gly	Pro	Ala	Val	Pro	Gly	Leu	Arg	Ala	Leu	Leu	Pro	Ala	Arg	Ala	Phe	
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Phe	Ile	Thr	Phe	Ile	Суз	Tyr	Val	Ala	Ser	Ser	Ala	Ser	Ala	Phe	Leu	
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Thr	Ala	Pro	Leu	Leu	Glu	Phe	Leu	Leu	Ala	Leu	Tyr	Phe	Leu	Phe	Ala	
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gat	gcc	atg	cag	ctg	aat	gac	aag	tgg	cag	ggc	ttg	tgc	tgg	CCC	atg	401
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Met	Asp	Phe	Leu	Arg	Сув	Val	Thr	Ala	Ala	Leu	Ile	Tyr	Phe	Ala	Ile	
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Asp Glu Thr Thr Ala His Lys Thr Glu Glu Glu Asn Ser Asp Ser Asp	
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Leu Glu Ala Lys Thr Gly Val Glu Lys Arg Tyr Leu Ala Ala Gly Ala	
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Val Thr Leu Leu Ser Leu Tyr Leu Leu Phe Gly Tyr Gly Ala Ser Leu	
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Ala Ile Glu Ser Pro Ser Lys Asp Asp Asp Thr Val Trp Leu Thr Tyr 75 80 85	
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Trp Val Val Tyr Ala Leu Phe Gly Leu Ala Glu Phe Phe Ser Asp Leu	Ū
90 95 100	
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Leu Leu Ser Trp Phe Pro Phe Tyr Tyr Val Gly Lys Cys Ala Phe Leu	•
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Leu Phe Cys Met Ala Pro Arg Pro Trp Asn Gly Ala Leu Met Leu Tyr	
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Arg Ile Met Asn Asp Leu Ser Gly A	Arg Ala Leu Asp Ala	Ala Ala Gly
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Met Ser Arg Phe Leu 1 5	_	o rip Leu
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Val Met Val Ser Ile Ile Ala Met G	TA Was Jul Den GIU	per tile wid

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Asp His Thr Phe Leu Tyr Glu Lys Leu Tyr Thr Gly Lys Pro Asn Leu	
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Val Asn Gly Leu Gln Ala Arg Thr Phe Gly Ile Trp Thr Leu Leu Ser	
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Ser Val Ile Arg Cys Leu Cys Ala Ile Asp Ile His Asn Lys Thr Leu	
65 70 75	
tat cac atc aca etc tgg acc tte etc ett gec etg ggg cat tte etc	408
Tyr His Ile Thr Leu Trp Thr Phe Leu Leu Ala Leu Gly His Phe Leu	
80 85 90	
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Ser Glu Leu Phe Val Tyr Gly Thr Ala Ala Pro Thr Ile Gly Val Leu	
95 100 105	
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Ala Pro Leu Met Val Ala Ser Phe Ser Ile Leu Gly Met Leu Val Gly	
110 115 120	
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Leu Arg Tyr Leu Glu Val Glu Pro Val Ser Arg Gln Lys Lys Arg Asn	
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Val Met Asn Ser Arg Gly Met Trp Leu Thr Tyr Ala Leu Gly Va	
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Ala Trp Thr Leu Thr Asn Ile Ile His Asn Leu Gly Met Tyr Va	il Phe
50 55 60	
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Leu His Ala Val Lys Gly Thr Pro Phe Glu Thr Pro Asp Gln Gl	ly Lys
65 70 75	469
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Ala Arg Leu Leu Thr His Trp Glu Gln Leu Asp Tyr Gly Val Gl	
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Thr Ser Ser Arg Lys Phe Phe Thr Ile Ser Pro Ile Ile Leu Ty	_
100 105 11	
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Leu Ala Ser Phe Tyr Thr Lys Tyr Asp Pro Thr His Phe Ile Le	u asn
115 120 125	

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Thr Ala Ser Leu Leu Ser Val Leu Ile Pro Lys Met Pro Gln Leu His	
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Gly Val Arg Ile Phe Gly Ile Asn Lys Tyr	
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Phe Leu Ile Gln Thr Lys Asp Asn Pro Met Lys Ala Val Gly Val Leu	
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Ala Gly Thr Met Ala Thr Val Val Ala Ile Thr Val Leu Ile Ser Thr	
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Ala	Thr	Phe	Trp	Arg	Asn	Lys	Lys	Ser	Asn	Lys	Val	Leu	Pro	Met	Arg	
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Arg	Val	Leu	Arg	Lys	Arg	Pro	Ser	Pro	Ala	Pro	Arg	Thr	Ile	Arg	Ile	
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Glu	Trp	Leu	Lys	Ser	Lys	Ser	Thr	Lys	Ala	Ala	Thr	Lys	Phe	Met	Leu	
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Lys	Glu	Lys	Pro	Pro	Asn	Glu	Asn	Сла	Asn	Asn	Asn	Ser	Pro	Glu	Ser	
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Leu	Thr	Pro	Gln	Pro	Thr	Gln	Pro	Pro	Pro	Lys	Pro	ГЛа	Thr	Met	Gly	
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Lys	Lys	Ser	Val	His	Asn	Lys	Ala	Tyr	Phe							
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Gln Arg Asp	_	Ala Ile	Ser Met	Phe Leu	_	Leu Leu	
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gee ace ate t				_			301
Ala Thr Ile I	Phe Leu Asp	Ile Val	His Ile	Ser Ile	Phe Tyr	Pro Arg	
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Gly	Asn	Leu	Asp	Leu	Glu	Ala	Phe	Val	Leu	Met	Ala	Ala	Glu	Ile	Gly
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Arg	Thr	Thr	Tyr	Lys	Gly	Phe	Thr	Glu	Ala	Val	qaA	Leu	Tyr	Phe	Asp
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His	Leu	Met	Ser	Arg	Val	Val	Pro	Leu	Gln	Tyr	Lys	Arg	Gly	Gly	Pro
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Ile	Val	Gln	Gly	Val	Leu	Ala	Thr	Ile	Asn	Leu	Gln	Ser	Thr	His	Glu
				245					250					255	
Leu	Gln	Leu	Leu	Thr	Thr	Phe	Leu	Phe	Asn	Val	Gln	Gly	Thr	Gln	Pro
			260					265					270		
Lys	Met	Val	Met	Glu	Tyr	Trp	Thr	Gly	Trp	Phe	Asp	Ser	Trp	Gly	Gly
		275					280					285			
Pro	His	Asn	Ile	Leu	Asp	Ser	Ser	Glu	Val	Leu	ГÀз	Thr	Val	Ser	Ala
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305					310					315					320
The	Aan	Dhe	Glw	Dhe	Mot	λen	Glv	A 7 a	Mot	uio	Dhe	Hie	Agn	ጥነም	Lva

				325					330					335	į.
Ser	Asp	Val	Thr	Ser	Tyr	Asp	Tyr	Asp	Ala	Val	Leu	Thr	Glu	Ala	Gly
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Asp		Gly	Gln	Val	Phe		Asn	Thr	Val	Ser		Gly	Phe	Leu	Asp
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-1 -	•	•	-1.	485	_		_		490	•	<u>-</u>		•	495	•
TTE	Asp	Asp	Gln	Arg	rys	GTÀ	Leu		GIÀ	Asn	Leu	ıyr	Leu 510	Asn	Asp
Core	D	T	500	3	nh -	3	T1 -	505		T	3	<b>\</b>		T	c
per	PIO		Lys	ASN	Pne	Arg		TYE	ser	Leu	Азр	525	гЛя	гур	ser
Dho	Pho	515	200	Dho	C3	T 011	520	T	m	502	50×		Dro	Glu.	
FIIG	530	GIII	Arg	Pile	GTÀ	535	Asp	туз	пр	SeT	540	Ten	PLO	GIU	1111
Dro	_	Leu	Pro	פות	Dho		T en	Clv	Sor	Ten		Tle	Ser	Ser	ጥኮኮ
545	1111	Dea	FIU	ALG	550	FIIG	Leu	СТХ	Ser	555	Pet	TT-	561	DOT	560
	Cva	Aan	Thr	Dho		Taro	Len	GI 12	Clv		GI 11	Tare	Glw	t/al	
110	Cys	- Yap	1111	565	Leu	пуз	Leu	GIU	570	ırp	GIU	пλэ	GIŞ	575	Val
Dho	Tla	) co	Gly		) an	Lou	C1++	7-4		<b>Ш</b>	7 cn	T10	Glv.		Gla
- 11 <del>C</del>	176	NOII	580	<b>GTII</b>	WOII	neu	GLY	585	<b>-</b>	TTP	wali		590	£10	GLII
Twe	ጥኮ፦	T.e.11	Tyr	T.eu	Dro	G1••	Dro		T.o.13	Sor	Ser			Δοη	G] n
ny s	7111	505	TÅT	nen	£T.O	атÃ	EUU FIO	тъ	Ten	PRT	DET	euz Già	TTG	nali	GIII

Val	Ile	Val	Phe	Glu	Glu	Thr	Met	Ala	Gly	Pro	Ala	Leu	Gln	Phe	Thi
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Leu	Tyr	Met	Ala	Ala	Pro	Gln	Ile	Arg	Lys	Met	Leu	Ser	Ser	Gly	Va]
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Cys	Thr	Ser	Thr	Val	Gln	Leu	Pro	Gly	Lys	Val	Val	Val	Val	Thr	Gly
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Arg	Lys	Leu	Asp	Leu	Ser	Asp	Thr	Lys	Ser	Ile	Arg	Ala		Ala	Lys
			100					105					110		_
Gly	Phe	Leu	Ala	Glu	Glu	ГÀз	His	Leu	His	Val	Leu		Asn	Asn	Ala
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Glu	Lys	Phe	Tyr	Asn	Ala	Gly	Leu	Ala	Tyr	Сув	His	Ser	Lys	Leu	Ala

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Ile	Glu	Gly	Ile	Asn	Arg	Gly	Leu	Ser	Asn	Ala	Glu	Arg	Glu	Val	Gly
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Val	Glu	Lys	Val	Phe	Asn	Gly	Leu	Ser	Asn	Met	Gly	Ser	His	Thr	Gly
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Lys	Glu	Leu	Asp	ГÀЗ	Gly	Val	Gln	Gly	Leu	Asn	His	Gly	Met	qeA	Lys
				85					90					95	
Val	Ala	His	Glu	Ile	Asn	His	Gly	Ile	Gly	Gln	Ala	Gly	Lys	Glu	Ala
			100					105					110		
Glu	Lys		Gly	His	Gly	Val		Asn	Ala	Ala	Gly		Ala	Gly	Lys
_	_	115		_		_	120					125		_	
Glu		qeA	Lys	Ala	Val		Gly	Phe	His	Thr	_	Val	His	Gln	Ala
	130					135					140		- <b>-</b>		_
-	Lys	Glu	Ala	Glu	-	Leu	Gly	Gln	Gly		Asn	His	Ala	Ala	
145		<b>~</b> 3.	_		150			_		155			•	•	160
GIN	Ala	GIĀ	Lys		Val	GLu	ГЛЯ	Leu		GIN	GTĀ	ALA	H18		ATG
	<b>01</b>	<b>01</b>	•••	165	<b>-</b>	<b>0</b> 7	•	<b>-1</b>	170	.1.	<b></b> .	•	<b>0</b> 1	175	
Ala	GIY	GIN		GIÀ	гла	GIU	Leu		Asn	ALA	HIS	ASN		vaı	Asn
<b>a</b> 1-	n1_	0	180	<b>0</b> 1	.1_	•	a1	185	<b>-</b>	•		•	190	<b>~</b> 1	C
GIU	AIA		Lys	GIU	ATS	ASN		Leu	Leu	ASN	ĠТĀ		HIS	GIII	ser
<b>63</b>	C	195	0	***	a1-	03	200		<b>50</b> 1	<b>m</b> la aa	ml	205	<b>.</b>		C
Gly		ser	ser	HIS	GTD	_	СΤĀ	ATS	TNI	TUL		LIO	ьeu	АТЯ	ser
	210	0	**- 7	<b>&gt;</b>	<b>-</b>	215	-1	_,	•	<b>-</b>	220	<b>-1</b> -	<b>.</b>	<b>m</b>	N
Gly	WTG	ser	vaT			PTO	Lue	TTG			7Ľ0	WTØ	ren	ırp	
225	17-1	<b>3</b> 7-	N am		230	<b></b>				235					240

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245

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Ala	Ala	Ala	Ser	Ser	Gly	Leu	Arg	Phe	Val	Leu	Ala	Ser	Phe	Ala	Leu
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Pro	Trp	Val		Val	Arg	Gly	Ser	Gly	Asp	Val	Сув	Gly		Leu	Ala
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Ser		Ser	Arg	Trp	His		Arg	Arg	Gly	Val		Arg	Arg	Leu	Leu
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	Phe	Ala	Glu	Ala		Ala	Arg	Ala	Trp		Gly	Gly	Met	Gly	
145		_			150			_		155			_		160
Pro	Arg	Ala	Arg		Val	Val	Pro	Val	Ala	Val	Ala	Ala	Trp		Val
				165					170	_	_	_ <b>_</b> .		175	
Gly	Gly	Met		Glu	Gly	Сув	Gly		Gln	Ala	Glu	Gly		Trp	GIŸ
_	_		180		_			185			_	_	190		
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			20					25					30		
Gln	Leu	Trp	Phe	Phe	Arg	Phe	Val	Val	Asn	Ala	Ala	Gly	Tyr	Ala	Ser
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Phe	Met	Val	Pro	Gly	Tyr	Leu	Leu	Val	Gln	Tyr	Phe	Arg	Arg	Lys	Asn
	50					55					60				
Tyr	Leu	Glu	Thr	Gly	Arg	Gly	Leu	Суз	Phe		Leu	Val	Lys	Ala	Суз
65					70					75				_	80
Val	Phe	Gly	Asn		Pro	Lys	Ala	Ser		Glu	Val	Pro	Leu		Pro
			_	85	_				90					95	
Arg	Thr	Glu		Ala	Glu	Thr	Thr		Met	Trp	Gln	Ala		ГЛа	Leu
_		_	100			_		105		_	_		110	-1	
Leu	Pne	_	Ala	Thr	Gly	Leu		Val	Ser	Tyr	Leu		лтр	GIĀ	Val
<b>T</b>	<b>~</b> 1~	115		•••		mb	120		<b>.</b>	<b>03-</b> -	<b>31</b> -	125		mh	Com
ren		GIU	Arg	val	Met		Arg	ser	туr	GIÀ		The	Ala	THE	Ser
D	130	<b>61</b>	<b>.</b>	<b>7</b> h -	m\	135	0	<b>6</b> 1-	Dh -	T	140	T 011	Wot	A an	N~~
145	GIY	GIU	ALG	Pne	Thr	Авр	Set	GIU	Pne	155	vaı	Den	Mec	Vali	160
	Tou	פות	Tou	Tlo	150 Val	*1.		Tou	Sor.		wal	T.OII	Cve	T.ve	
var	Leu	Ma	Tien	165	vai	MIG	GTĀ	Deu	170	cys	var	Tien	CJS	175	GIII.
Dro	Δνα	uia	Glv		Pro	Mo+	(Treated	Ara		Ser	Dhe	Δla	Ser		Ser
110	n.y	1113	180	ALG	FIO	Mec	TYL	185	+ <b>Y</b> -	Del	<b>F110</b>	******	190		
Δan	t/a1	T.e.11		Sor	Trp	وري	Gln		Glu	λla	Teu	T.V9		Val	Ser
21011	Vul	195	<b>5</b> 61	Der	112	Cys	200	-y-	GIU	ALU.	20.4	205			
Phe	Pro		Gln	บลไ	Leu	Δla		Ala	Sor	T.VQ	Val		Pro	Val	Met
	210	***	<b>U</b> 111	VUL	LCu	215	בעב	mu	<b>0</b> 01	2,5	220			·	
Ten		G]v	Lva	Len	Val		Ara	Ara	Ser	ጥህጉ		His	Tro	Glu	Tvr
225		,	-,-		230					235			<b>F</b>		240
	ጥከተ	Δla	ጥኮተ	T.em		Ser	Tle	Glv	Va1		Met	Phe	Leu	Leu	Ser

245

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250

255

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Phe	Ala	Ala	His	Ala	Leu	Leu	Leu	Ser	Ile	Cys	Ser	Ala	Cys	Gly	Gln
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Val	Thr	Ala	Gly	Thr	Pro	Glu	Val	Trp	Val	Gln	Val	Arg	Met	Glu	Ala
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Thr	Glu	Leu	Ser	Ser	Phe	Thr	Ile	Arg	Суз	Gly	Phe	Leu	Gly	Ser	Gly
		35					40					45			

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				85					90					95	
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			100					105					110		
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	210					215					220		_		
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225			_	_	230	•		_	_	235	_	_	_		240
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Ala Ser Asp Asp Pro Ile Glu Lys Val Ile Glu Gly Ile Asn Arg Gly									
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Ser Gly Ile Thr His Ala Gly Arg Glu Val Glu Lys Val Phe Asn Gly 60 65 70									
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Leu Gln Asn	Ala His Asn (Gly Val Asn	Gln Ala Ser Lys	Glu Ala Asn
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Leu	Leu	Leu	Leu	Ala	Ala	Ala	Ser	Ser	Gly	Leu	Arg	Phe	Val	Leu	Ala	
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Phe Met Val Pro Gly Tyr Leu Leu Val Gln Tyr Phe Arg Arg Lys Asn	
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Val	Phe	Gly	Asn	Glu	Pro	Lys	Ala	Ser	Asp	Glu	Val	Pro	Leu	Ala	Pro	
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cga	aca	gag	gcg	gca	gag	acc	acc	ccg	atg	tgg	cag	gcc	ctg	aag	ctg	453
Arg	Thr	Glu	Ala	Ala	Glu	Thr	Thr	Pro	Met	Trp	Gln	Ala	Leu	Lys	Leu	
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ctc	ttc	tgt	gcc	aca	999	ctc	cag	gtg	tet	tat	ctg	act	tgg	ggt	gtg	501
Leu	Phe	Сув	Ala	Thr	Gly	Leu	Gln	Val	Ser	Tyr	Leu	Thr	Trp	Gly	Val	
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Leu	Gln	Glu	Arg	Val	Met	Thr	Arg	Ser	Tyr	Gly	Ala	Thr	Ala	Thr	Ser	
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ccg	ggt	gag	cgc	ttt	acg	gac	tcg	cag	ttc	ctg	gtg	cta	atg	aac	cga	597
Pro	Gly	Glu	Arg	Phe	Thr	Asp	Ser	Gln	Phe	Leu	Val	Leu	Met	Asn	Arg	
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Val	Leu	Ala	Leu		Val	Ala	Gly	Leu	Ser	Сув	Val	Leu	Cys		Gln	
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Pro	Arg	His	Gly	Ala	Pro	Met	Tyr		Tyr	Ser	Phe	Ala		Leu	Ser	
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Asn	Val		Ser	Ser	Trp	Сув		Tyr	Glu	Ala	Leu		Phe	Val	Ser	
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Phe	Pro	Thr	Gln	Val	Leu	Ala	Lys	Ala	Ser	Lys		Ile	Pro	Val	Met	
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	Met	Gly	Lys	Leu		Ser	Arg	Arg	Ser	_	Glu	His	Trp	Glu		
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ctg	aca	gcc	aca	ctc	atc	tee	att	<b>333</b>	gtc	agc	atg	ttt	ctg	cta	tee	885
Leu	Thr	Ala	Thr	Leu	Ile	Ser	Ile	Gly	Val	Ser	Met	Phe	Leu	Leu	Ser	
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Ser	Gly	Pro	Glu	Pro	Arg	Ser	Ser	Pro	Ala	Thr	Thr	Leu	Ser	Gly	Leu	
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Ile	Leu	Leu	Ala	Gly	Tyr	Ile	Ala	Phe	Asp	Ser	Phe	Thr	Ser	Asn	Trp	
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Gln	Asp	Ala	Leu	Phe	Ala	Tyr	Lys	Met	Ser	Ser	Val	Gln	Met	Met	Phe	
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Gln	Gly	Ala	Leu	Leu	Glu	Gly	Thr	Arg	Phe	Met	Gly	Arg	His	Ser	Glu	
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Phe	Ala	Ala	His	Ala	Leu	Leu	Leu	Ser	Ile	Сув	Ser	Ala	Суз	Gly	Gln	
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Leu	Phe		Phe	Tyr	Thr	Ile	Gly	Gln	Phe	Gly	Ala		Val	Phe	Thr	
		355					360					365				
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Ile		Met	Thr	Leu	Arg	Gln	Ala	Phe	Ala	Ile	Leu	Leu	Ser	Сла	Leu	
	370					375					380					
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	Tyr	Gly	His	Thr	Val	Thr	Val	Val	Gly	_	Leu	Gly	Val	Ala		
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Val	Phe	Ala	Ala		Leu	Leu	Arg	Val	_	Ala	Arg	Gly	Arg		Lys	
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			aag			-		_								1413
Gln	Arg	Gly	Lys	Lys	Ala	Val	Pro	Val	Glu	Ser	Pro	Val	Gln	Lys	Val	
			420					425					430			
			aggg				_	_	-	-						1470
~+~~	+ ~+ *	80.0	teta	2000	9 77	+ ~~	tass	900	7779	aat	acea	atat	<b>++ +</b>	ctca	atate	1530

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gactgtaggg ggcc atg ggg cac cgg acc ctg gtc ctg ccc tgg gtg ctg  Met Gly His Arg Thr Leu Val Leu Pro Trp Val Leu  1 5 10  ctg acc ttg tgt gtc act gcg ggg acc ccg gag gtg tgg gtt caa gtt  Leu Thr Leu Cys Val Thr Ala Gly Thr Pro Glu Val Trp Val Gln Val  15 20 25  cgg atg gag gcc acc gag ctc tcg tcc ttc acc atc cgt tgt ggg ttc  Arg Met Glu Ala Thr Glu Leu Ser Ser Phe Thr Ile Arg Cys Gly Phe	110 158
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Ser	Ile	Ser	Leu	Ile	Leu	Glu	Gly	Ser	Gly	Ala	Ser	Ser	Pro	Суз	Ala	
		95					100					105				
aac	acc	acc	ttc	tgc	tgc	aag	ttt	geg	tcc	ttc	cct	gag	ggc	tcc	tgg	446
Asn	Thr	Thr	Phe	Cys	Сув	Lys	Phe	Ala	Ser	Phe	Pro	Glu	Gly	Ser	Trp	
	110					115					120					
gag	gcc	tgt	<b>9</b> 99	agc	ctc	ccg	ccc	agc	tca	gac	cca	999	ctc	tct	gcc	494
Glu	Ala	Суз	Gly	Ser	Leu	Pro	Pro	Ser	Ser	Asp	Pro	Gly	Leu	Ser	Ala	
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Pro	Pro	Thr	Pro	Ala	Pro	Ile	Leu	Arg	Ala	Asp	Leu	Ala	Gly	Ile	Leu	
				145					150					155		
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Gly	Val	Ser	Gly	Val	Leu	Leu	Phe	Gly	Суз	Val	Tyr	Leu	Leu	His	Leu	
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Leu	Arg	Arg	His	Lys	His	Arg	Pro	Ala	Pro	Arg	Leu	Gln	Pro	Ser	Arg	
		175					180					185				
acc	agc	ccc	cag	gca	ccg	aga	gca	cga	gca	tgg	gca	cca	agc	cag	gec	686
Thr	Ser	Pro	Gln	Ala	Pro	Arg	Ala	Arg	Ala	Trp	Ala	Pro	Ser	Gln	Ala	
	190					195					200					
tcc	cag	gct	gct	ctt	cac	gtc	cct	tat	gcc	act	atc	aac	acc	agc	tgc	734
Ser	Gln	Ala	Ala	Leu	His	Val	Pro	Tyr	Ala	Thr	Ile	Asn	Thr	Ser	Сув	
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cgc	cca	gct	act	ttg	gac	aca	gct	cac	ccc	cat	ggg	<b>9</b> 99	ccg	tcc	tgg	782
Arg	Pro	Ala	Thr	Leu	Asp	Thr	Ala	His	Pro	His	Gly	Gly	Pro	Ser	Trp	
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Trp	Ala	Ser	Leu	Pro	Thr	His	Ala	Ala	His	Arg	Pro	Gln	Gly	Pro	Ala	
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gcc	tgg	gcc	tcc	aca	ccc	atc	cct	gca	cgt	ggc	agc	ttt	gtc	tct	gtt	878
Ala	Trp	Ala	Ser	Thr	Pro	Ile	Pro	Ala	Arg	Gly	Ser	Phe	Val	Ser	Val	
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Glu Asn Gly Leu Tyr Ala Gln Ala Gly Glu Arg Pro Pro His Thr Gly	
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ccc ggc ctc act ctt ttc cct gac cct cgg ggg ccc agg gcc atg gaa	974
Pro Gly Leu Thr Leu Phe Pro Asp Pro Arg Gly Pro Arg Ala Met Glu	
285 290 295 300	
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Gly Pro Leu Gly Val Arg	
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Met Gln Ser Cys Glu Ser Ser Gly Asp Ser	
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Ala Asp Asp Pro Leu Ser Arg Gly Leu Arg Arg Gly Gln Pro Arg	
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Val Val Val Ile Gly Ala Gly Leu Ala Gly Leu Ala Ala Ala Lys Ala	
30 35 40	
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His	Ile	Gly	Gly	Arg	Val	Gln	Ser	Val	Lys	Leu	Gly	His	Ala	Thr	Phe	
	60					65					70					
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Glu	Leu	Gly	Ala	Thr	Trp	Ile	His	Gly	Ser	His	Gly	Asn	Pro	Ile	Tyr	
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His	Leu	Ala	Glu	Ala	Asn	Gly	Leu	Leu	Glu	Glu	Thr	Thr	qeA	Gly	Glu	
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-	-			-	atc	_				_				-	-	569
Arg	Ser	Val	Gly	Arg	Ile	Ser	Leu	Tyr	Ser	Lys	Asn	Gly	Val	Ala	Сув	
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tac	ctt	acc	aac	cac	ggc	cgc	agg	atc	CCC	aag	gac	gtg	gtt	gag	gaa	617
Tyr	Leu		Asn	His	Gly	Arg	Arg	Ile	Pro	Lys	Asp	Val	Val	Glu	Glu	
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Phe	Ser	qeA	Leu	Tyr	Asn	Glu	Val	Tyr	Asn	Leu	Thr	Gln	Glu	Phe	Phe	
	140					145					150					
					gtc		_	_	_							713
_	His	Asp	Lys	Pro	Val	Asn	Ala	Glu	Ser		Asn	Ser	Val	Gly		
155					160					165					170	
		_			gtg	•		_				_				761
Phe	Thr	Arg	Glu		Val	Arg	Asn	Arg		Arg	Asn	qeA	Pro		Asp	
				175					180					185		
				_	cgc	-	_		-	_						809
Pro	Glu	Ala		Lys	Arg	Leu	ГЛЗ		Ala	Met	Ile	Gln		Tyr	Leu	
			190					195					200			
			_	-	gag	_	_			_	_	-				857
Lys	Val		Ser	Сув	Glu	Ser		Ser	His	Ser	Met	Asp	Glu	Val	Ser	
		205					210					215				
					gag						-					905
Leu	Ser	Ala	Phe.	Gly	Glu	Trp	Thr	Glu	Ile	Pro	Gly	Ala	His	His	Ile	
	220					225					230					

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Ile	Pro	Ser	Gly	Phe	Met	Arg	Val	Val	Glu	Lev	Leu	Ala	Glu	Gly	Ile	
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Pro	Ala	His	Val	Ile	Gln	Leu	Gly	Lys	Pro	Val	Arg	Cys	Ile	His	Trp	
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gac	cag	gcc	tca	gcc	aga	ccc	aga	ggc	cct	gag	att	gag	ccc	cgg	ggt	1049
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Val	Glu	Cys	Glu	Asp	Суз	Glu	Leu	Ile	Pro	Ala	qeA	His	Val	Ile	Val	
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Thr	Val	Ser	Leu	Gly	Val	Leu	Lys	Arg	Gln	Tyr	Thr	Ser	Phe	Phe	Arg	
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cca	ggc	ctg	ccc	aca	gag	aag	gtg	gat	gcc	atc	cac	cgc	ctg	ggc	att	1289
Pro	Gly	Leu	Pro	Thr	Glu	Lys	Val	Ala	Ala	Ile	His	Arg	Leu	Gly	Ile	
			350					355					360			
			-	-			_	-	ttc							1337
Gly	Thr		Asp	Lys	Ile	Phe	Leu	Glu	Phe	Glu	Glu	Pro	Phe	Trp	Gly	
		365					370					375				
									tgg							1385
Pro	Glu	Cys	Asn	Ser	Leu	Gln	Phe	Val	Trp	Glu	Asp	Glu	Ala	Glu	Ser	
	380					385					390	~				
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His	Thr	Leu	Thr	Tyr	Pro	Pro	Glu	Leu	Trp	Tyr	Arg	Lys	Ile	Суз	Gly	
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Phe	Asp	Val	Leu	Tvr	Pro	Pro	Glu	Ara	Tvr	Glv	His	Val	Leu	Ser	Glv	

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Trp	Ile	Суз	Gly	Glu	Glu	Ala	Leu	Val	Met	Glu	Lys	Сув	Asp	qeA	Glu	
			430					435					440			
gca	gtg	gcc	gag	atc	tgc	acg	gag	atg	ctg	cgt	cag	tta	aca	ggg	aac	1577
Ala	Val	Ala	Glu	Ile	Сув	Thr	Glu	Met	Leu	Arg	Gln	Phe	Thr	Gly	Asn	
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Pro .	Asn	Ile	Pro	Lys	Pro	Arg	Arg	Ile	Leu	Arg	Ser	Ala	Trp	Gly	Ser	
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aac	cct	tac	ttc	cgc	ggc	tee	tat	tca	tac	acg	cag	gtg	ggc	tcc	age	1673
Asn :	Pro	Tyr	Phe	Arg	Gly	Ser	Tyr	Ser	Tyr	Thr	Gln	Val	Gly	Ser	Ser	
475					480					485					490	
ggg (	gcg	gat	gtg	gag	aag	ctg	gcc	aag	ccc	ctg	ccg	tac	acg	gag	agc	1721
Gly 2	Ala	Asp	Val	Glu	Lys	Leu	Ala	Lys	Pro	Leu	Pro	Tyr	Thr	Glu	Ser	
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tca	aag	aca	gcg	ccc	atg	cag	gtg	ctg	ttt	tcc	ggt	gag	gcc	acc	cac	1769
Ser 1	Lys	Thr	Ala	Pro	Met	Gln	Val	Leu	Phe	Ser	Gly	Glu	Ala	Thr	His	
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cgc (	aag	tac	tat	tcc	acc	acc	cac	ggt	gct	ctg	ctg	tcc	ggc	cag	cgt	1817
Arg 1	Lys	Tyr	Tyr	Ser	Thr	Thr	His	Gly	Ala	Leu	Leu	Ser	Gly	Gln	Arg	
		525					530					535				
gag (	gct	gcc	aga	ctc	att	gag	atg	tac	cga	gac	ctc	ttc	cag	cag	ggg	1865
Glu A	Ala	Ala	Arg	Leu	Ile	Glu	Met	Tyr	Arg	qaA	Leu	Phe	Gln	Gln	Gly	
5	540					545					550					
acc t	tgag	ggct	gt c	ctcg	ctgc	t ga	gaag	agco	act	aact	cgt	gacc	tcca	ge e	t	1920
Thr						·									,	
555																
gece	ettg	ct g	ccgt	gtgc	t cc	tgcc	ttcc	tga	tcct	ctg	taga	aagg	at t	ttta	tette	1980
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Met Gly Ser Gln His Ser Ala	
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get get ege eee tee tee tge agg ega aag eaa gaa gat gae agg gae	161
Ala Ala Arg Pro Ser Ser Cys Arg Arg Lys Gln Glu Asp Asp Arg Asp	
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Gly Leu Leu Ala Glu Arg Glu Glu Glu Glu Ala Ile Ala Gln Phe Pro	
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Phe Phe Leu Phe Pro His Ser Val Leu Val Asp Asp Gly Ile Lys	
105 110 115	107
	197
Val Val Lys Val Thr Phe Asn Lys Gln Asp Ser Leu Val Ile Leu Thr 120 125 130 135	
120 125 130 135	

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Ile Met Ala Thr Leu Lys Ile Arg Asn Ser Asn Phe Tyr Thr Val Ala	
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gtg acc agc ctg tec agc cag att cag tac atg aac aca gtg gtc agt	593
Val Thr Ser Leu Ser Ser Gln Ile Gln Tyr Met Asn Thr Val Val Ser	
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aca tat gtg act act aac gtc tcc ctt att cca cct cgg agt gag caa	641
Thr Tyr Val Thr Thr Asn Val Ser Leu Ile Pro Pro Arg Ser Glu Gln	
170 175 180	
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Leu Val Asn Phe Thr Gly Lys Ala Glu Met Gly Gly Pro Phe Ser Tyr	
185 190 195	
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Ile Phe Met Arg Thr Ser Val Lys Ile Ser Tyr Ile Gly Leu Met Thr	
220 225 230	
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Gln Ser Ser Leu Glu Thr His His Tyr Val Asp Cys Gly Gly Asn Ser	
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Lys Gln Gly Val Ser Ala Lys Asn Gln Gly Ala His Asp Pro Asp Tyr					
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Glu Asn Ile Thr Leu Ala Phe Lys Asn Gln Asp His Ala Lys Gly Gly					
30 35 40					
cat toa oga oco acg ago caa gto oca geo cag tgo agg ocg oco toa	196				
His Ser Arg Pro Thr Ser Gln Val Pro Ala Gln Cys Arg Pro Pro Ser					
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gae tee ace cag gte eec tge tgg ttg tae aga gee ate etg age etg	244				
Asp Ser Thr Gln Val Pro Cys Trp Leu Tyr Arg Ala Ile Leu Ser Leu					
60 65 70					
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Tyr Ile Leu Leu Ala Leu Ala Phe Val Leu Cys Ile Ile Leu Ser Ala					
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Phe Ile Met Val Lys Asn Ala Glu Met Ser Lys Glu Leu Leu Gly Phe					
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Lys Arg Glu Leu Trp Asn Val Ser Asn Ser Val Gln Ala Cys Glu Glu					
110 115 120	40.0				
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Arg Gln Lys Arg Gly Trp Asp Ser Val Gln Gln Ser Ile Thr Met Val					

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Arg Ser Lys I	Ile Asp Arg Leu Glu	Thr Thr Leu Ala	Gly Ile Lys Asn
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Ile Asp Thr I	Lys Val Gln Lys Ile	Leu Glu Val Leu	Gln Lys Met Pro
155	160	165	
cag too toa o	ect caa taaatgagag g	acattgtgg cagcca	aagc cac 580
Gln Ser Ser P	Pro Gln		
170			
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